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British Heart Journal

A monthly journal of cardiology published in association with the British Cardiac Society

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British Heart Journal

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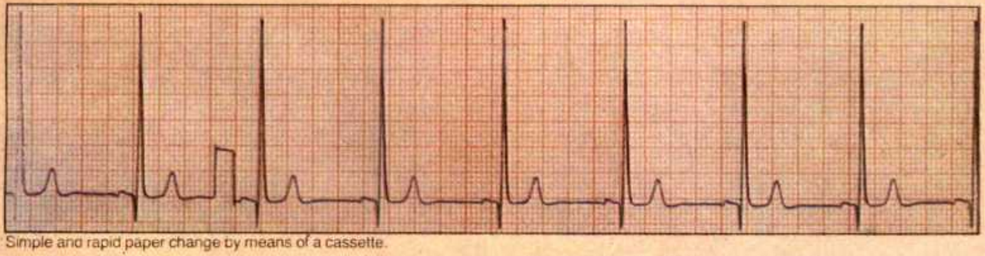

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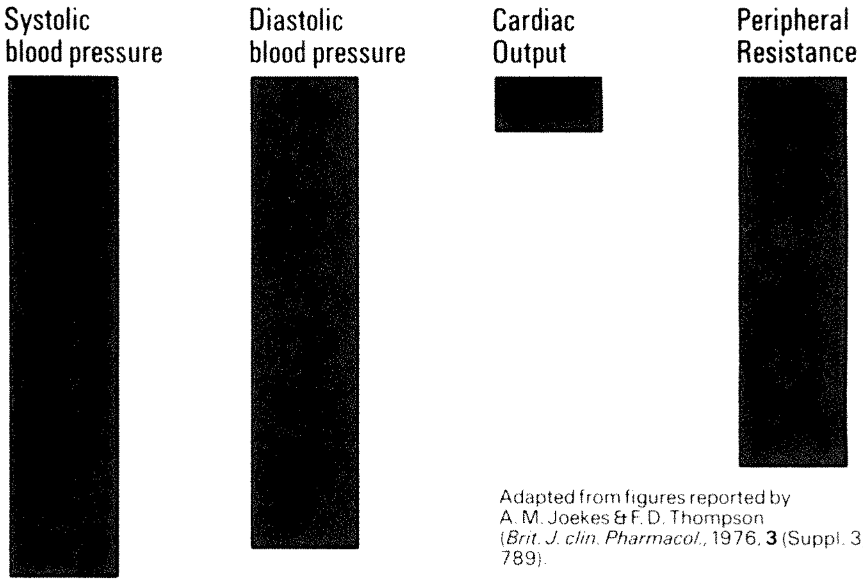

Adapted from figures reported by
A. M. Joekes & F. D. Thompson
(*Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 789).

The above figure shows the mean haemodynamic changes in 14 hypertensive patients given intravenous Trandate 0.5-1.0mg/kg

In essential hypertension the usual haemodynamic changes are increased blood pressure and peripheral resistance while cardiac output remains normal.

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"A practical advantage associated with labetalol is that oral treatment can be instituted immediately after using the intravenous form." (Rønne-Rasmussen, J. O. et al, *Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 805)

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Trandate Injection: 20ml ampoules each containing 100mg (5mg/ml) labetalol hydrochloride, in boxes of 5 ampoules. PL 0045/0104.

INDICATIONS

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Trandate Injection is indicated when rapid control of blood pressure is essential.

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Children: Not applicable.
For information on the use of Trandate with other drugs or for transfer to Trandate from other antihypertensive agents, see respective Data Sheets.

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Trandate should not be given to patients with uncontrolled or digitalis-resistant heart failure, or with atrioventricular block. Caution is necessary in asthmatic patients or others prone to bronchospasm. Patients with severe liver damage will probably require lower doses of Trandate than usual. Unnecessary administration of drugs during the first trimester of pregnancy is undesirable.
Trandate Injection may cause excessive postural hypotension if patients are allowed to assume the upright position within 3 hours of administration.
Trandate Tablets may cause symptoms of postural hypotension if initial dosage is too high or increased too rapidly, but they are uncommon, except at very high doses, if used as recommended. Mild and usually transient side effects include: headache, tiredness, dizziness, depressed mood, lethargy, difficulty in micturition, epigastric pain and nausea and vomiting. Tingling in the scalp has occasionally occurred but is usually transient. Rarely, a lichenoid rash has been reported which disappears on drug withdrawal. Other skin rashes, blurring of vision, eye irritation and cramps have been reported but have been difficult to relate directly to Trandate treatment.
Warning: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the drug was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta-adrenoceptor blocking drug should be gradual.

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Normal

Pericardial effusion.

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Normal

Tricuspid valve vegetation.

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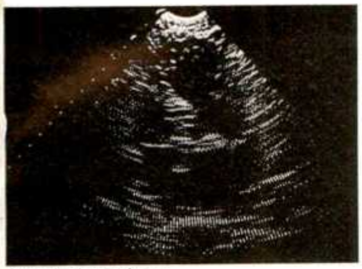
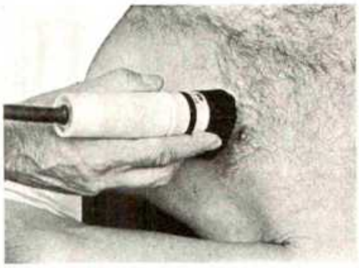
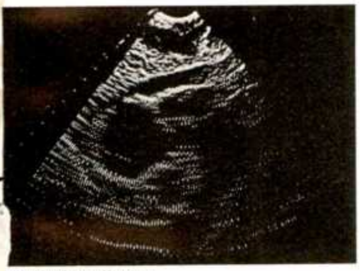


Mitral valve prolapse.

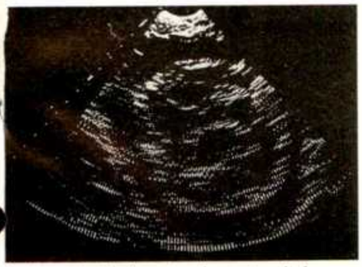


Apex Four Chamber Views



Pericardial effusion.

Subxyphoid Views



Left ventricular hypertrophy pericardial effusion, short axis.

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Many authorities agree that elevated serum cholesterol is an important factor in the development of atherosclerosis. And, while it is not yet possible to assume that lowering cholesterol will reduce morbidity from coronary heart disease, most physicians accept the importance of maintaining serum cholesterol levels as close to normal as possible.

Colestid (colestipol), a new non-systemic agent developed by Upjohn research, effectively lowers serum cholesterol by an average 12–15% in Type II hyperlipidaemic patients – those with elevated cholesterol and normal or slightly elevated triglycerides[1,2,3] A lowering of serum cholesterol by 19% has been demonstrated with 10 grams of Colestid given twice a day.

Colestid achieves a reduction in serum cholesterol by interfering with the normal enterohepatic circulation of bile acids. Bile acids are synthesised in the liver from cholesterol and are secreted in bile into the intestine. Colestid works in the intestinal lumen, binding these bile acids and increasing the rate of their excretion. Less bile acid is available for reabsorption from the intestine, and the liver must convert additional cholesterol to bile acid. The result is a reduction in plasma cholesterol levels.

Unlike other resin preparations, Colestid is well accepted by most patients. The odourless, tasteless granules may be mixed with a variety of liquids and foods, including fruit juices, milk, soups, pulpy fruits with a high water content, and carbonated beverages.

Colestid has produced no known interference with the action of coumarin anticoagulants, making it suitable for patients already under treatment for a heart condition. However, since Colestid may interfere with the absorption of certain drugs (e.g., chlorothiazide, tetracycline and penicillin G), the clinical response to concomitant medications should be closely monitored and appropriate adjustments made.

Most patients tolerate Colestid therapy very well. The most common side effect is mild constipation.

References: 1. Med. J. Aust. (1973) *1*:1223.
2. JAMA (1972). 222:676.
3. New Zealand J. Med. (1972). 76:12.

Prescribing Information

Presentations: Tasteless and odourless granules of colestipol hydrochloride. *Uses:* Adjunctive therapy to diet for treatment of hypercholesterolaemia, particularly Frederickson Type II. *Dosage and Administration:* Always mix with water or other fluids before ingesting. Oral total daily dosage for adult 15–30 grams. Take in divided doses 2–4 times daily. *Contraindications:* Hypersensitivity to colestipol. *Precautions, Warnings:* Not to be taken in dry form. Colestid may interfere with absorption of some drugs (e.g. penicillin G, tetracycline, chlorothiazide). Safety for use in pregnant women or children not established. *Package Quantities:* 30 x 5 g sachets; 250 g bottle. Each sachet or scoopful contains 5 g colestipol hydrochloride. *Further Information:* Colestid is not absorbed. It binds bile acids causing further cholesterol conversion to bile acids thus lowering serum cholesterol levels. *Basic NHS Costs:* 30 x 5 g sachets £8.90. 250 g bottle £13.76. Product Licence Nos. PL 0032/0055. PL 0032/0057. *Full Product information is available on request.*

history concerns us!

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1789

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Bologna

1901

The first radio signal to cross the Atlantic

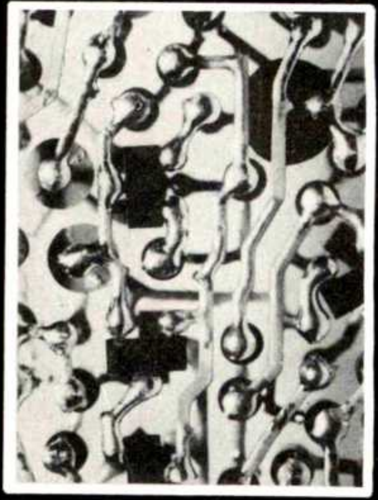
Guglielmo Marconi
(Bologna 1874-Roma 1937)

He is universally known for the invention of wireless telegraphy which served as the basis for research in radiophonic broadcasting. In 1909 he received the Nobel Prize for physics.

Bologna

1978

The latest achievement of modern technology



Biotec 776-777
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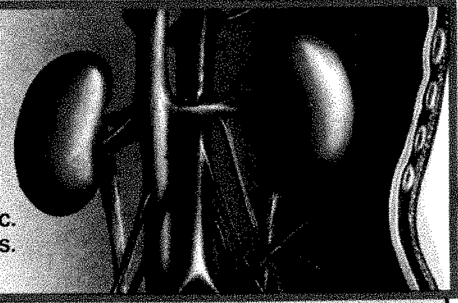

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[1] Data on file

5006 A–Jun 79

Corgard prescribing information

PRESENTATION

White, round, tablet engraved 'Squibb' and '241', scored on reverse, containing 80 mg nadolol.

Indications

For the long-term management of essential hypertension, either alone or in combination with other anti-hypertensive agents.

DOSAGE AND ADMINISTRATION

Initially 80 mg once daily. This dose may be increased by 80 mg increments at weekly intervals until an optimum response is obtained. Most patients respond to 240 mg or less, daily, but doses up to 640 mg have occasionally been used. In some patients it may be necessary to administer a diuretic, peripheral vasodilator and/or other anti-hypertensive agents in conjunction with nadolol in order to achieve satisfactory response. Dosage should be individually titrated.

Nadolol may be given in a once daily dosage without regard to meals.

Treatment of hypertension associated with phaeochromocytoma may require the addition of an alpha-blocking agent.

Contra-indications

Like other drugs in this class, nadolol is contra-indicated in bronchial asthma; allergic rhinitis during the pollen season; sinus bradycardia and 2nd and 3rd degree heart block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure; during and within 2 weeks of administration of adrenergic augmenting psychotropic drugs such as monoamine oxidase inhibitors.

Warnings

Exacerbation of angina and myocardial infarction have occurred after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with angina pectoris or other evidence of coronary artery insufficiency.

The normal precautions associated with the use of beta-adrenergic blockers should be followed.

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta-adrenergic blocker should be gradual.

Nadolol should be used with caution in patients with impaired renal or hepatic function.

The safety of nadolol in pregnancy has not yet been established, and it should only be given to nursing mothers if deemed essential.

Side-effects

These resemble those reported with other beta-blocking drugs and rarely require withdrawal of treatment. They include gastro-intestinal effects, bradycardia, fatigue, light-headedness, cold extremities, insomnia, paraesthesia and dryness of the mouth. Cardiac insufficiency, hypotension and AV block have occurred on rare occasions. Overdosage or exaggerated response should be treated supportively and symptomatically.

LEGAL CATEGORY

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Product Licence Number

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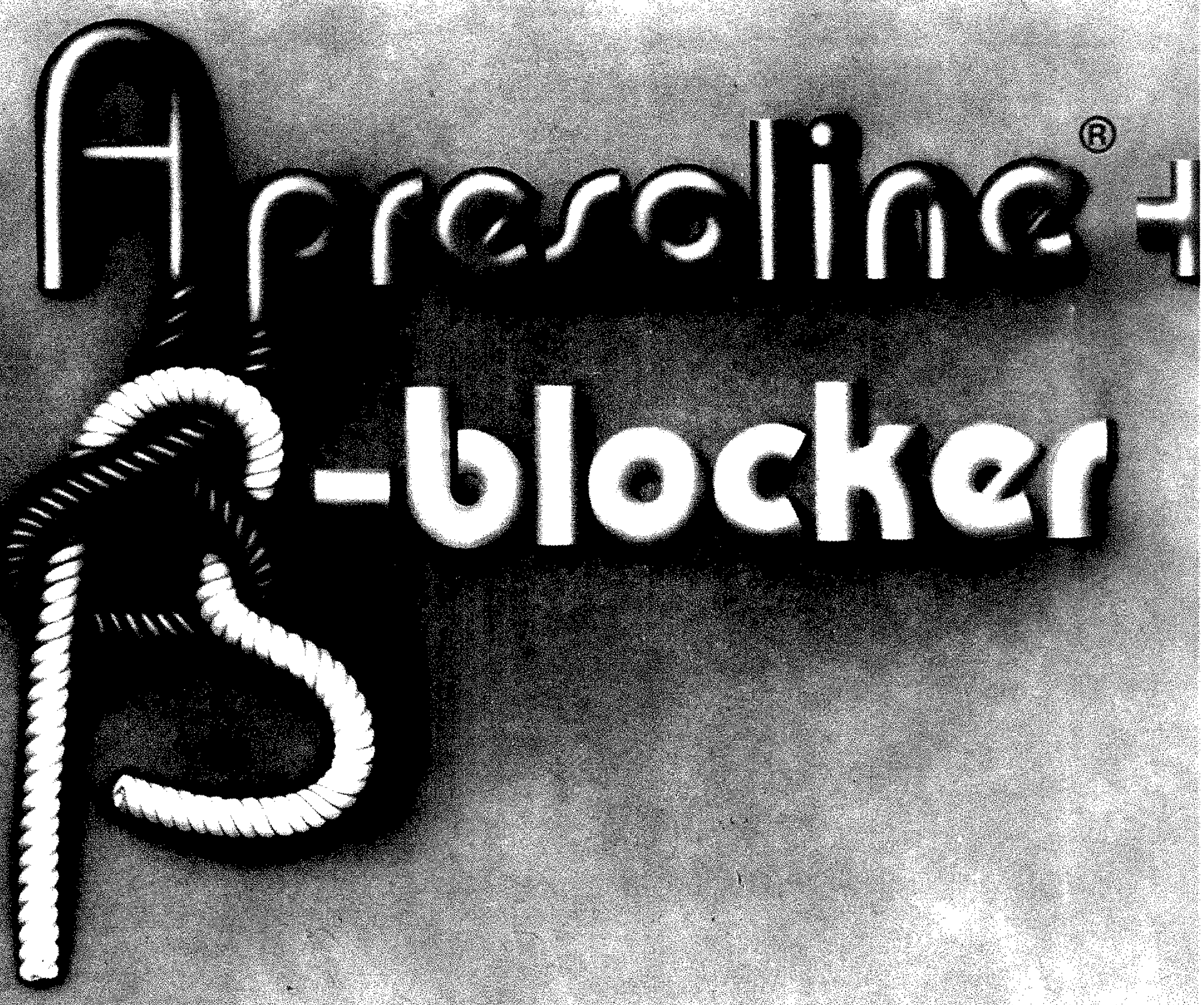
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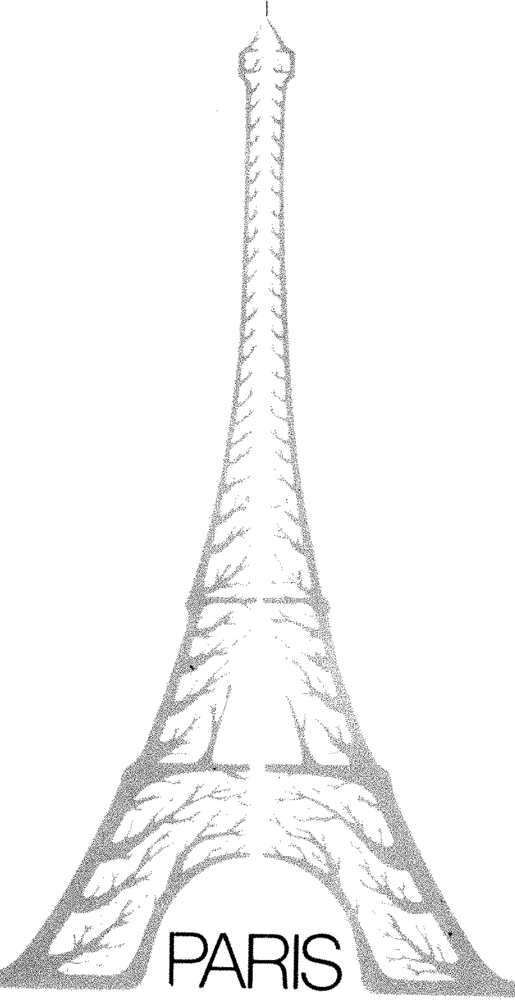

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Atrioventricular conduction tissues in univentricular hearts of left ventricular type with absent right atrioventricular connection ('tricuspid atresia')

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SUMMARY The atrioventricular conduction tissues in 14 hearts with absence of the right atrioventricular connection ('tricuspid atresia') were studied by serial sectioning. In all cases, the atrioventricular node lay in the floor of the right atrium, posterior to the tendon of Todaro, but in all but one case it extended anteriorly either medial or lateral to the insertion of the tendon in a way not seen in the normal heart. The common bundle frequently arose from the anterior or lateral extensions of the node and, after penetration of the central fibrous body, came to lie on the right wall of the main ventricular chamber at the point of junction with the septum separating this chamber from the outlet chamber. In all but 3 cases, branching of the bundle occurred posterior to the outlet foramen. The distribution of the left bundle characteristically favoured the posterior part of the main chamber and the right bundle passed inferior to the outlet foramen to ramify in the trabecular zone of the outlet chamber.

Although these findings differ in some respects from those previously described in univentricular hearts with an outlet chamber and 2 atrioventricular valves, we believe that they are consistent with our view that the majority of hearts with absence of the right atrioventricular connection come within the category of the univentricular heart.

In recent years, the outlook for patients with atresia or absence of the right atrioventricular orifice has been improved by the use of corrective surgical procedures such as that developed by Fontan and Baudet (1971). During such procedures, the conducting tissue may be at risk during closure of the atrial septal defect, during closure of the outlet foramen, and when enlargement of the outlet foramen is required because the aorta arises from the outlet chamber. The disposition of conducting tissue also has implications for the morphology and classification of the anomaly.

Anderson and his colleagues (1977) have expressed the view that atresia (or absence) of the right atrioventricular orifice is, in most cases, associated with the ventricular morphology of a univentricular heart, usually with an anterior rudimentary chamber. They recognised, however, that in a small number of cases an imperforate tricuspid membrane interposed between the right atrium and a formed right ventricle (Anderson *et al.*, 1977; Dickinson *et al.*, 1979). On the other hand, Bharati *et al.* (1976) considered the anterior chamber in 'tricuspid atresia' to be a true right ventricle in all cases. More recently (Bharati and Lev, 1977) they have used their findings regarding the distribution of the conducting tissue in the anomaly to support this view.

We have now examined the conducting system in 14 cases of absence of the right atrioventricular orifice. Our results are here discussed with particular reference to the nomenclature of the anomaly, to the implications for surgical treatment, and to the electrocardiographic findings.

Materials and methods

The specimens studied were taken from the pathological collections of the Royal Liverpool Children's Hospital and the Wilhelmina Gasthuis, Amsterdam.

After study of the morphological features and

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photography, tissue blocks were taken to include the lower part of the floor of the right atrium, the interatrial septum, the orifice of the coronary sinus, and the base of the ventricular mass including portions of the main ventricular chamber, the anterior chamber, the intervening septum, and the roots of the great arteries. The blocks were embedded in paraffin wax, sectioned at 10 μm thickness and stored according to our established practice (Smith *et al.*, 1977). Initially each fiftieth section was stained using a modification of Masson's technique. Intermediate sections were prepared and stained from areas of special interest.

Reconstructions of specimens 1 and 7 were prepared by projection of each fiftieth section onto 6 mm Plastazote sheets with a magnification factor of × 12. The projected image was traced, cut out, and coloured to distinguish the histological features. The sheets could then be assembled in an accurate reconstruction of the original tissue block.

Results

The main morphological features of the specimens are described in Table 1. The electrocardiographic findings in 7 of the cases are presented in Table 2.

Situs solitus with laevocardia was present in all cases, with normal systemic and pulmonary venous drainage to the right and left atrium, respectively. In each specimen the right atrium was blind ending, the only outlet being via a defect in the interatrial septum (Fig. 1). This took the form of a secundum atrial septal defect in 7 cases and a widely patent foramen ovale in 6 cases. Where a dimple was present in the floor of the atrium, transillumination disclosed a potential connection only with the main ventricular chamber.

One specimen (case 7) differed from the others in that there was a cleft in the anterior leaflet of the mitral valve. The atrial septal defect extended down to the mitral annulus (Fig. 2). Examination of the ventricular septal morphology showed a small but well-defined smooth surfaced septum extending to the crux of the heart (Fig. 3A). Anteriorly this was continuous with the trabecular septum which separated the main and rudimentary chambers. The small 'inlet' septum subdivided the main chamber into a minute crevice and the major compartment which received the left atrioventricular valve and had left ventricular trabecular characteristics. The outlet chamber was in communication only with the main chamber via a small outlet foramen at the junction of the smooth 'inlet' septum with the trabecular septum (Fig. 3A). The morphology of the outlet chamber in this case was similar to that seen in the other cases and there was no communi-

Table 1 *Morphological features*

Case	*Situs*	*Dimple*	*Atrial septum*	*Outlet chamber*	*Aorta from outlet chamber*	*Pulmonary artery from outlet chamber*
1	S	+	PFO	R	0	+
2	S	0	Sec	R	0	+
3	S	+	Sec	R	0	+
4	S	0	Sec	R	0	+
5	S	+	PFO	R	0	+
6	S	0	PFO	R	0	+
7	S	+	Prim	R	0	+
8	S	0	Sec	R	0	+
9	S	+	PFO	R	0	+
10	S	+	PFO	R	+	0
11	S	+	Sec	Anterior	+	0
12	S	0	PFO	R	+	0
13	S	+	Sec	R	0*	+
14	S	+	Sec	R	+	0

*The aorta was left sided and anterior ('anatomically corrected malposition').
+, Present; 0, Absent; Prim, primum atrial septal defect; Sec, secundum atrial septal defect; PFO, patent foramen ovale; S, solitus.

Table 2 *Electrocardiographic features*

Case	*Rhythm*	*PR interval*	*QRS axis*	*QRS duration*	*Comments*
1	Sinus	0·10	− 40°	0·06	Q in aVL but not in V6
3	Sinus	0·09	0°	0·07	
5	Sinus	0·09	− 10°	0·06	
6	Sinus	0·08	− 40°	0·06	
7	Sinus	0·11	− 10°	0·06	No septal Q in V6 or aVL
8	Sinus	0·10	− 10°	0·08	
12	Sinus	0·10	+ 60°	0·08	No septal Q in V6 or aVL

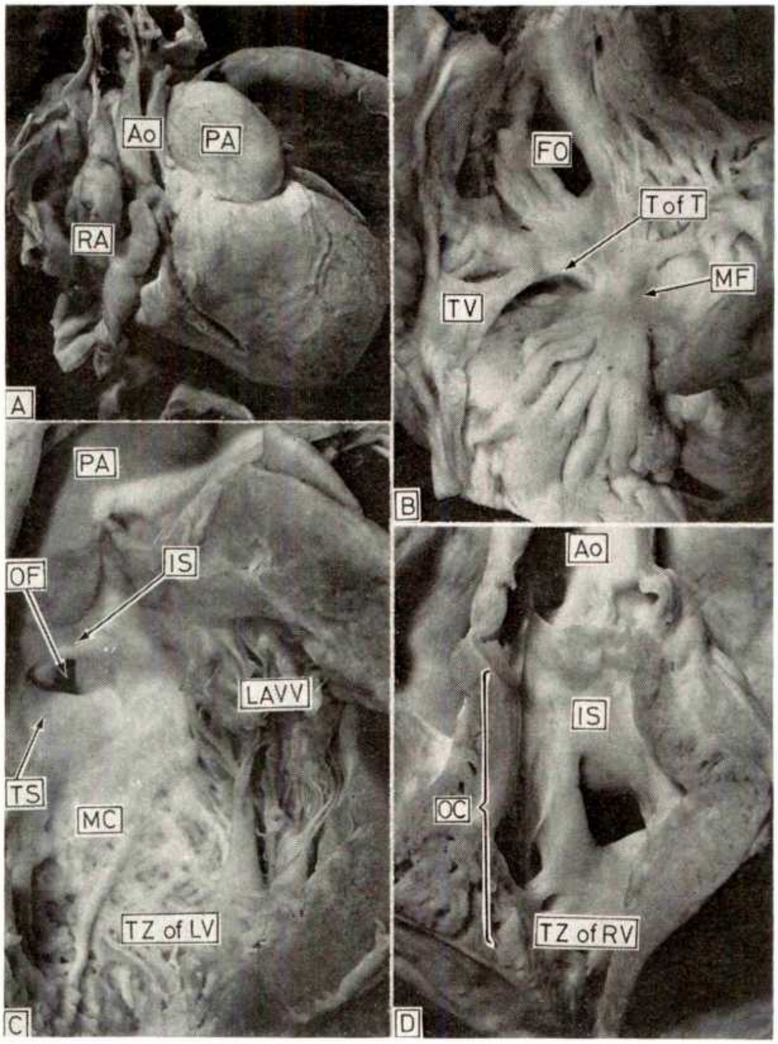

Fig. 1 *(A) The external appearance of case 14 viewed from the anterior aspect. The aorta arises from an outlet chamber on the right anterior shoulder of the ventricular mass. (B) The right atrium of case 14. (C) The main ventricular chamber of case 14. (D) The outlet chamber of case 14.*
Ao, aorta; PA, pulmonary artery; RA, right atrium; FO, foramen ovale; T of T, tendon of Todaro; MF, muscular floor of right atrium; TV, Thebesian valve; MC, main chamber; OC, outlet chamber; OF, outlet foramen; LAVV, left atrioventricular valve; IS, infundibular septum; TS, trabecular septum; TZ of LV, trabecular zone of left ventricular type; TZ of RV, trabecular zone of right ventricular type.

cation between the 'outlet chamber' and the hypoplastic crevice.

HISTOLOGY (Table 3)

In all cases the atrioventricular node occupied a constant position in the floor of the atrium in close or intimate relation with the central fibrous body. The dimple, when present, lay anterolateral and immediately adjacent to the node. The main body of the node lay posterior to the insertion of the tendon of Todaro in all cases, but was in direct contact with the right atrioventricular sulcus (Fig. 4A). In

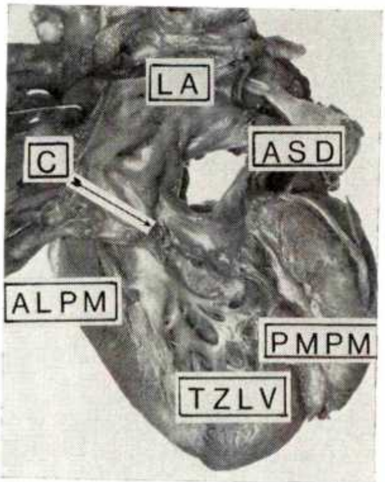

Fig. 2 *The left atrium and main ventricular chamber of case 7, showing a large atrial septal defect extending to the left atrioventricular annulus. The cleft in the left atrioventricular valve is indicated. LA, left atrium; C, cleft; ASD, atrial septal defect; TZLV, trabecular zone of left ventricular type; PMPM, posteromedial papillary muscle; ALPM, anterolateral papillary muscle.*

all 13 cases, the node extended anteriorly, either medial or lateral to the insertion of the tendon, and in 9 of these cases the penetrating bundle took origin from this anterior extension. In case 7, the atrioventricular node was situated immediately adjacent to the hypoplastic posterior rim of the atrial septal defect, and the right atrium was potentially in connection with the 'crevice' previously described.

After penetration of the central fibrous body (Fig. 4C) the common bundle came to lie on the right parietal wall of the main ventricular chamber at the point of junction with the septum separating the main chamber from the outlet chamber (Fig. 4D). In this proximal position the bundle was buried within the myocardium, and only in case 7 did the bundle lie on the crest of the septum as it does in a normally septated heart.

In this case the perforating bundle lay on the crest of the septum between the main chamber and the 'crevice' previously described (Fig. 3B). The bifurcation of the bundle in this case, as in the majority of the remaining cases, lay posterior to the outlet foramen (Fig. 5). In cases 2, 4, and 13, branching of the main bundle occurred at the posteroinferior margin of the outlet foramen. A left bundle-branch was present in all cases and characteristically favoured the posterior part of the trabecular septum and the septal-parietal wall junction. In cases 7 and 12 the left bundle-branch was relatively poorly developed and connection with the main bundle, though present, was tenuous. From the point of branching, the right bundle took an intramuscular course, inferior to the outlet foramen. The right bundle-branch was poorly developed in case 10 and was absent in cases 6, 9, and 13.

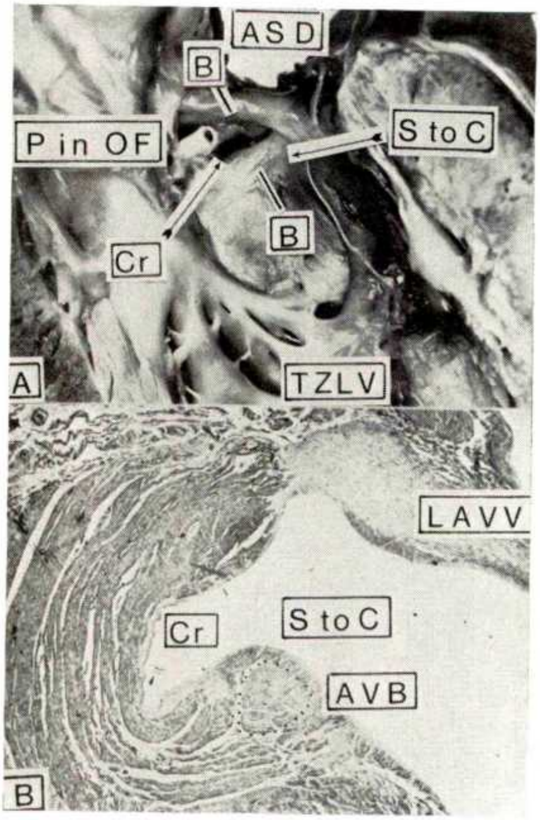

Fig. 3 (*A*) *The main ventricular chamber of case 7. The left atrioventricular valve has been detached from the posteromedial papillary muscle and reflected through the atrial septal defect. ASD, atrial septal defect; P in OF, probe in outlet foramen; Cr, crevice; S to C, septum extending to the crux of the heart. B-B plane of section in Fig. 3B. TZLV, trabecular zone of left ventricular type.* (*B*) *Photomicrograph of case 7 showing the atrioventricular bundle on the crest of the septum between the main chamber and the crevice. Cr, crevice; AVB, atrioventricular bundle; LAVV, left atrioventricular valve; S to C, septum to crux of heart.*

Discussion

Our results show an abnormal disposition of the atrioventricular conducting tissue in hearts with 'classical tricuspid atresia'. The atrioventricular

Table 3 *Histological features of conducting tissue*

Case	*Atrioventricular node*	*Perforation*	*Common bundle*		*Left bundle-branch*	*Right bundle-branch*
			Relation to OF	*Bifurcation*		
1	Well formed; extends anterolateral to tendon	From lateral extension	Well posterior	Posterior to OF	Mainly posterior distribution	Well formed
2	Hypoplastic; best seen anterolateral to tendon	Anterior to tendon	Posterior and inferior	Inferior rim of OF	Mainly posterior distribution	Poor proximal development
3	Well developed; some extension lateral to tendon	Posterior to tendon	Posterior but close	Posterior to OF	Mainly posterior distribution	Well formed
4	Extensive; seen medial and lateral to tendon	From lateral extension	Inferior	Inferior rim of OF	Mainly posterior distribution	Well formed
5	Well developed; extends medial and anterior to tendon	Posterior to tendon	Posterior and inferior	Posterior to OF	Evenly distributed	Poor proximal development
6	Well developed; small extension medial to tendon	Posteromedial to tendon	Posterior	Posterior to OF	Mainly posterior distribution	Not seen
7	Well developed; extends lateral to tendon	From lateral extension	Well posterior	Posterior to OF	Mainly posterior distribution	Well developed
8	Well developed; with lateral and medial extensions	Posterior to tendon	Posterior	Posterior to OF	Widely distributed	Well developed
9	Well formed; extends lateral to tendon	From lateral extension	Posterior	Posterior to OF	Mainly posterior distribution	Not seen
10	Well developed posterior to tendon	Posterior to tendon	Posterior	Posterior to OF	Mainly posterior distribution	Poor proximal development
11	Well developed; some lateral extension	From lateral extension	Posterior	Close to inferior rim of OF	Widely distributed	Well developed
12	Well developed with anterolateral extension	From anterolateral extension	Posterior	Posterior to OF	Poorly developed	Poorly developed
13	Well developed; extends lateral to tendon	From anterolateral extension	Posterior but close to margin	Posterior rim of OF	Widely distributed	Not seen
14	Well developed; extends anterior and lateral to tendon	Anterior to tendon	Posterior	Posterior to OF	Widely distributed	Well developed

Tendon, tendon of Todaro; OF, outlet foramen.

node was closely related to the tendon of Todaro in all cases, so that from the right atrial aspect the node had a relatively normal position. However, in all cases it was related to the right atrioventricular sulcus rather than the posterior sulcus as in the normal heart (Fig. 6). Furthermore, in 13 cases the node extended anteriorly beyond the point of insertion of the tendon of Todaro into the central fibrous body. It then descended onto ventricular myocardium which constituted the parietal free wall at the site of junction with the septum separating the outlet chamber from the main ventricular chamber.

Although these observations do not differ greatly from the findings of Guller *et al.* (1969) and Bharati and Lev (1977), there are significant differences in interpretation. Bharati and Lev (1977) contrasted the posteriorly situated atrioventricular node seen in 'tricuspid atresia', with the anteriorly situated node and conducting pathway seen in univentricular hearts of left ventricular type with outlet chamber. They used this in support of their view that 'tricuspid atresia' is not a variant of the univentricular heart, arguing that if it were, then an anteriorly located node and conducting pathway should be anticipated. We have previously suggested (Anderson *et al.*, 1974) that the absence of a posterior conduction pathway in double inlet univentricular hearts of left ventricular type was related to absence of a posterior inlet septum extending to the crux of the heart. When the right atrioventricular connection is absent, as in classical 'tricuspid atresia', then the inlet septum is almost invariably absent. The acute margin of the heart necessarily approximates to the crux (Fig. 6). In this situation, whatever the position of the node localised in the floor of the right atrium it will be able to make contact with conduction tissue in the anterior trabecular septum. Moreover, in the univentricular heart with a formed right atrioventricular orifice, the various areas of specialised tissue from which a conducting pathway may arise are separated by the valve orifice. If such a valve orifice is totally absent these different areas will be aggregated into a confluent zone. Thus, the anticipated anterior node of the univentricular heart of left ventricular type will be approximated to and be confluent with the anticipated site of the regular node. There is, therefore, no possibility in classical 'tricuspid atresia' of a separate anterior node and connection. In several of our specimens the penetrating bundle took origin from the anterolateral portion of the nodal aggregation, anterior to the insertion of the tendon of Todaro. This, in our opinion, is entirely compatible with the arrangement of conducting tissue seen in the univentricular heart of left ventricular type with 2 atrioventricular ostia.

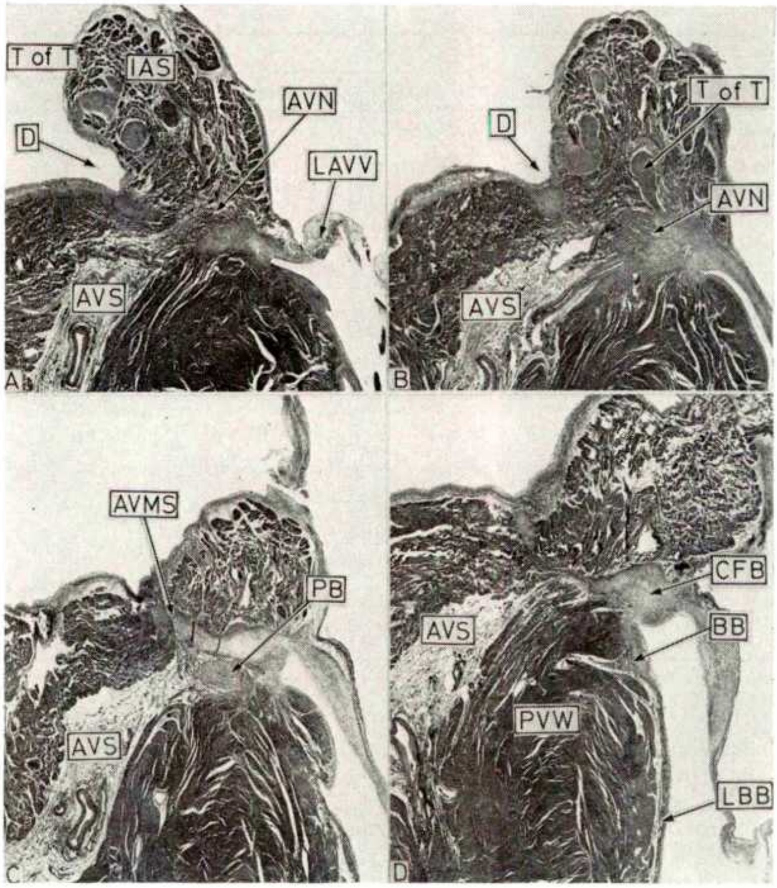

Fig. 4 *The atrioventricular conducting tissue of case 14. (A) A well-formed atrioventricular node is present posterior to the insertion of the tendon of Todaro and related to the right atrioventricular sulcus. (B) The tendon of Todaro is seen at the point of insertion into the central fibrous body. A well-developed lateral extension to the node is present extending anteriorly to connect with the penetrating bundle. (C) The common bundle is seen after penetration of the central fibrous body. (D) The bundle now lies on the parietal ventricular wall and is seen at the point of division into left and right bundle-branches. T of T, tendon of Todaro; AVN, atrioventricular node; IAS, interatrial septum; D, dimple in right atrium; LAVV, left atrioventricular valve; AVMS, atrioventricular membraneous septum; PB, penetrating bundle; AVS, atrioventricular sulcus; PVW, parietal ventricular wall; BB, branching bundle (at the point of origin of the right bundle-branch); LBB, left bundle-branch.*

When we consider the distribution of conducting tissue within the ventricular mass, our findings in hearts with absent right atrioventricular connection are virtually identical with those previously reported in univentricular hearts of left ventricular type with double inlet connection (Anderson *et al.*, 1974; Bharati and Lev, 1975). They differ considerably from hearts with atrioventricular concordance but an imperforate tricuspid membrane (Dickinson *et al.*, 1979). In these latter specimens the conducting tissue is directly comparable with that seen in isolated ventricular septal defect (compare Fig. 5A, 6B).

Case 7 serves merely to emphasise these contentions. It possessed a hypoplastic 'inlet' septum separating a tiny crevice from the main body of the ventricular chamber. We interpreted this crevice as representing an unexpanded but discrete 'right ventricular inlet portion'. The location of the

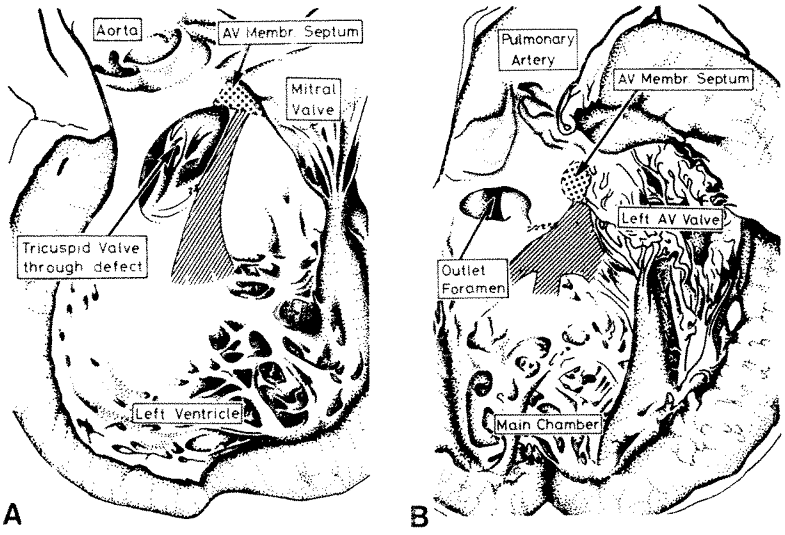

Fig. 5 (*A*) *Diagram of the distribution of conducting tissue within the left ventricle of a heart with atrioventricular concordance and a ventricular septal defect. Note the central position of the origin of the left bundle-branch on the septum.* (*B*) *Diagram of the conducting tissue in the main ventricular chamber of a univentricular heart of left ventricular type with absence of the right atrioventricular orifice. The orientation of this diagram corresponds to the orientation of the specimen in Fig. 1C. Note the displacement of the left bundle-branch posteriorly relative to the septum.*

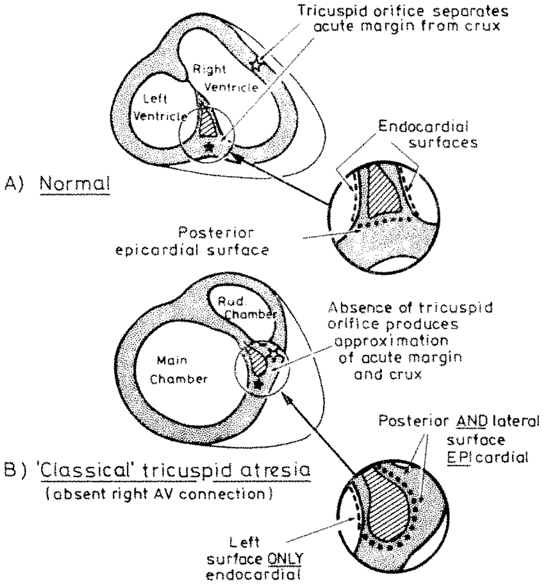
Tricuspid orifice separates acute margin from crux
Right Ventricle
Left Ventricle
Endocardial surfaces
A) Normal
Posterior epicardial surface
Rud Chamber
Main Chamber
Absence of tricuspid orifice produces approximation of acute margin and crux
Posterior AND lateral surface EPIcardial
B) 'Classical' tricuspid atresia
(absent right AV connection)
Left surface ONLY endocardial

Fig. 6 (*A*) *Diagram to illustrate the relations of the atrioventricular node in the normal heart. The body of the node sits astride the inlet ventricular septum and is related at its posterior extremity to the posterior atrioventricular sulcus. The tricuspid orifice separates the acute margin of the heart (open star) from the crux (closed star).* (*B*) *Diagram to illustrate the relations of the atrioventricular node in the univentricular heart with absence of the right atrioventricular orifice. The node is related to the right atrioventricular sulcus and absence of the tricuspid valve results in approximation of the acute margin to the crux of the heart.*

bundle on the crest of the septum between it and the body of the main chamber confirmed this interpretation. There was no communication between the crevice and the outlet chamber, which in all respects resembled that seen in the other specimens. As would have been expected, the right atrium was in potential connection with the hypoplastic 'right ventricular inlet portion'. We submit that these findings endorse our view (Anderson *et al.*, 1977) that the anomaly is unequivocally a univentricular heart.

SURGICAL IMPLICATIONS

The major significance to the surgeon of a detailed knowledge of the atrioventricular conduction tissues in classical 'tricuspid atresia' relates first to the position of the atrioventricular node within an atrium with abnormal geometry and secondly to the relation of the bundle and its branches to the outlet foramen. It is important, therefore, to appreciate that the atrioventricular node is in close relation to the tendon of Todaro, which is a readily identifiable landmark during surgical exposure. In addition the node lies immediately adjacent to the 'dimple', if present, in the floor of the right atrium. Where the inferior limbus of the atrial septal defect is deficient, as in case 7, the atrioventricular node may be extremely vulnerable to damage during closure of the defect.

The penetrating bundle and its branches may be at risk during procedures that involve the outlet foramen. It should be remembered that the bundle lies on the main chamber aspect of the trabecular septum and usually divides posterior to the outlet foramen. Occasionally, the branching bundle may be in close proximity to the posteroinferior rim of the foramen and the right bundle-branch may lie subendocardially in the rim of the defect. From these findings it seems probable that enlargement of the outlet foramen by resection of its anterior and superior margin would be unlikely to jeopardise the conduction system. Similarly, closure of the foramen should usually be accomplished safely provided that deep sutures are not placed in the posteroinferior quadrant.

Previous authors have suggested that an abnormality of the left bundle-branch might explain some of the characteristic electrocardiographic findings in hearts with absence of the right atrioventricular orifice. An anomalous course of the left bundle-branch was suspected by Gamboa *et al.* (1966) and this concept was supported by the findings of Guller *et al.* (1969). Our findings are in keeping with those of Guller *et al.* (1969) and further support the concept of an abnormal distribution of the left bundle-branch. We did not observe any bundle-branch fibrosis as suggested by Puri and Neill (1966). However, in a number of our cases the bundle-branches were hypoplastic and this may have influenced the sequence of ventricular activation, particularly in case 12.

A counterclockwise, superiorly orientated frontal plane QRS loop may result from asynchronous activation of the left ventricle. Early activation of the posterior left ventricular wall has been demonstrated in ostium primum atrial septal defect by Durrer *et al.* (1966) and Boineau *et al.* (1973). The abnormal distribution of the left bundle-branch seen in our cases of absence of the right atrioventricular orifice might similarly lead to early activation of the posterior ventricular wall. However, the typical electrocardiographic findings were also seen in 2 of the cases with atrioventricular concordance and imperforate tricuspid membrane (Dickinson *et al.*, 1979) even though in these latter cases well-developed anterior and posterior radiations of the left bundle-branch were present. Our studies suggest that in any heart with absence or atresia of the right atrioventricular orifice, shortening or absence of the posterior portion of the septum may lead to the posterior displacement of the bifurcation of the bundle relative to the ventricular mass as a whole.

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Atresia of the right atrioventricular orifice with atrioventricular concordance

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SUMMARY Three hearts are described in which a fibrous membrane was interposed between the right atrium and a formed but hypoplastic right ventricle, which possessed recognisable inlet, trabecular, and infundibular components. In these hearts the distribution of the conducting tissue was as expected for concordant atrioventricular connections, and contrasts with that seen in the classical type of 'tricuspid atresia'. The distinctive morphological and histological features of these specimens lend further support to our view that the majority of cases of atresia of the right atrioventricular orifice should be regarded as coming within the designation of 'the univentricular heart'.

Opinion is divided regarding the morphology of the ventricular chambers in hearts with 'tricuspid atresia'. Bharati and her colleagues (1976) stated that the anomaly should be considered as a variant of the hypoplastic right heart complex, comparable to hearts with tricuspid stenosis and pulmonary atresia with intact ventricular septum. More recently, Bharati and Lev (1977a) have studied the conducting tissue in these hearts and used their findings in support of this opinion. By contrast, Anderson *et al.* (1977), while agreeing that some cases of 'tricuspid atresia' had hypoplastic right ventricles, argued that the majority were univentricular hearts, the anterior chamber being a rudimentary chamber of right ventricular type comparable to that seen in 'single ventricle with outlet chamber'. We have recently studied 3 cases of 'tricuspid atresia' associated with left juxtaposition of the atrial appendages which are pertinent to this issue.

Since the description of a single case by Birmingham (1893), juxtaposition of the atrial appendages (Dixon, 1954) has been described in association with severe congenital cardiac malformations by many authors (Melhuish and Van Praagh, 1968). Atresia of the right atrioventricular orifice was present in 6 of the 21 new cases and 7 of the 21 previously reported cases reviewed by Melhuish and Van Praagh (1968). Our 3 cases are of particular interest because a potential connection existed between the right atrium and a formed but hypoplastic right ventricle, in contrast to the situation in the majority of cases of 'tricuspid atresia' where the potential connection is with the 'left ventricle' (Rosenquist *et al.*, 1970; Anderson *et al.*, 1977).

Material and methods

The 3 specimens studied were from the pathological collections of the Royal Liverpool Children's Hospital and the Brompton Hospital, London. All died of causes related to their cardiac condition at ages ranging from 2 weeks to 2 months. After morphological study, tissue blocks, including the atrioventricular junctional area were prepared and embedded in paraffin wax. The blocks were sectioned at 10 μm thickness. Initially, 1 section in 50 was stained using a modification of Masson's technique (Smith *et al.*, 1977). Intermediate sections were prepared and examined from areas of special interest.

Reconstructions of 2 of the blocks were made by projecting the stained sections on to 6 mm Plastazote sheets with a magnification factor of × 12. The outline was traced and cut out and the pieces coloured to identify the histological features. The pieces could then be assembled in an accurate reconstruction of the original tissue block.

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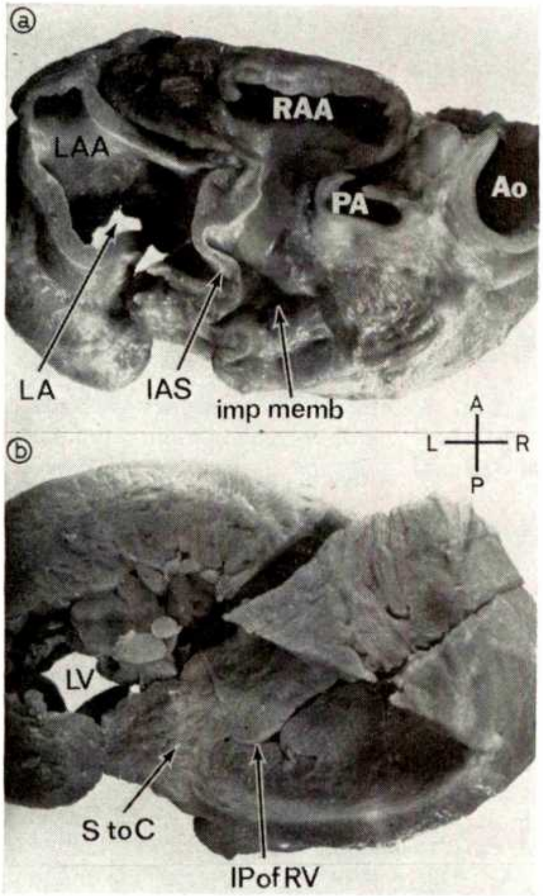

Fig. 1 (*a*). *Case 3 viewed from above showing the floor of the right atrium and the relation of the juxtaposed atrial appendages to each other and to the great arteries. The position of the imperforate 'tricuspid' membrane is indicated (b). The ventricular mass of case 3 viewed from below. The slit-like inlet portion of the right ventricle is indicated. The picture has been reversed photographically so as to retain the same orientation as for Fig. 1a.*
PA, pulmonary artery, Ao, aorta; LA, left atrium; LV, left ventricle; IP of RV, inlet portion of right ventricle; LAA, left atrial appendage; RAA, right atrial appendage; IAS, interatrial septum; imp memb, imperforate tricuspid membrane; S to C, septum to crux of heart.

Results

Visceroatrial situs solitus with laevocardia was present in all cases. The right atrium was blind ending, but in each case a discrete dimple was present in the floor of the right atrium, taking the form of a deep recess in case 3 (Fig. 1). In cases 1 and 2, transillumination of the specimen from the venricular mass showed an area of translucency between the main chamber and the right atrial dimple. Immediately adjacent to this was a smaller area of translucency related to the small inlet area of the right ventricle (Fig. 2).

The main ventricular chamber in all cases showed the morphological characteristics of a left ventricle, possessing an inlet via a mitral valve with paired papillary muscles. The interventricular communication was large in cases 2 and 3 but restrictive in case 1. Its posterior margin was the area between the mitral and pulmonary valves, the pulmonary artery arising from the left ventricle in all 3 specimens. Fibrous continuity between these valves was present only in case 3. A small but discrete inlet septum extended posteriorly to the crux of the heart (Fig. 1 and 3). This arrangement is unlike the morphology of the outlet foramen seen in the majority of cases of 'tricuspid atresia'.

The small inlet portion of the right ventricle could be traced towards the right atrial dimple and possessed fine trabeculations (Fig. 1 and 3). The trabecular zone of the chamber was more coarsely trabeculated and extended down the right shoulder of the venricular mass. A smooth-walled infundibulum was present in all the hearts and supported the aorta (Fig. 3b).

The histological findings (Table) in all 3 cases confirmed that the right atrial dimple separated the atrial chamber from the right ventricle. The dimple was an imperforate fibrous membrane extending

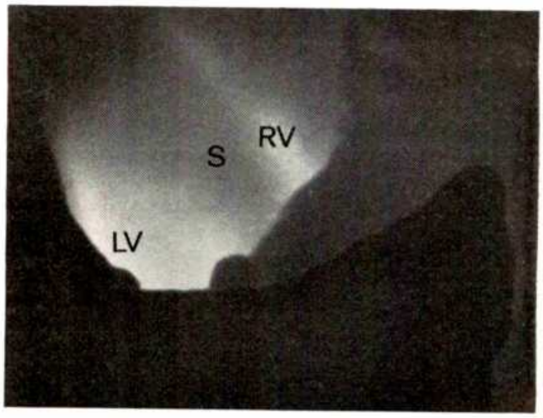

Fig. 2. *View of the right atrium of case 1 when transilluminated from the ventricular mass. Two areas of translucency are seen corresponding to the inflow area of the right ventricle and the atrioventricular component of the membraneous septum separating the right atrium from the left ventricular outflow tract. LV, left ventricle; RV, right ventricle; S septum.*

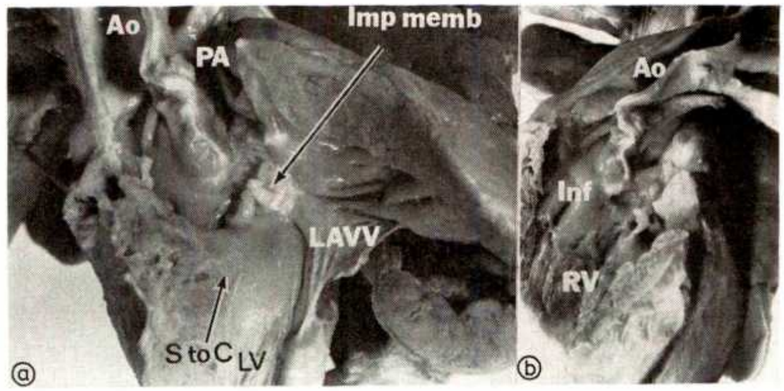

Fig. 3. (*a*). *View of the left ventricle of case 3. The imperforate 'tricuspid' membrane is seen to the right of the smooth surfaced septum which extends to the crux of the heart.* (*b*) *View of the right ventricle of case 3 showing the hypoplastic inlet zone, a trabecular zone, and a smooth walled infundibulum, supporting the aorta. Ao, aorta; PA, pulmonary artery; LV, left ventricle; RV, right ventricle; Inf, infundibulum; LAVV, left atrioventricular valve; S to C, septum to crux of heart; Imp memb, imperforate tricuspid membrane.*

from the atrial septum to the lateral atrioventricular sulcus, and in all respects was a miniature but imperforate 'tricuspid' valve. The atrioventricular node was disposed in normal fashion in the atrial septum, with the imperforate membrane lateral to it (Fig. 4). The atrioventricular bundle penetrated at the apex of the triangle of Koch, and immediately descended on to the inlet ventricular septum, where, in cases 2 and 3, it branched into typical right and left bundle-branches (Fig. 5). In case 1 a branching bundle was not identified, the penetrating bundle being hypoplastic and merging with ventricular myocardium soon after penetrating through the fibrous anulus. Bundle-branches were identified astride the septum further anteriorly but no connection between the main bundle and either the right or left branch could be identified.

Discussion

Cases of 'tricuspid atresia' have usually been excluded by definition from the category of the univentricular heart (Van Praagh *et al.*, 1964). This view has been challenged on angiographic grounds by Macartney *et al.* (1976), and on morphological grounds by Quero (1970). Lev *et al.* (1969) pointed to the importance of the site of the undeveloped right ventricular inlet component and its relation to the atretic right atrial orifice. Our studies have confirmed the importance of this feature. At that time Lev *et al.* (1969) conceded that hearts with 'tricuspid atresia' and transposition (aorta from outlet chamber) might be considered in the category of the univentricular heart, but more recently (Bharati *et al.*, 1976), they appear to have retracted from this

Table *Right atrioventricular orificial atresia with atrioventricular concordance features of conducting tissue*

	Atrioventricular node	*Common bundle*				*Left bundle-branch*	*Right bundle-branch*
		Subendocardial	*Intramuscular*	*Relation to ventricular septal defect*	*Bifurcation*		
1	Well formed with ant. extension	0	+	Barely enters myocardium	Absent	Sparse but even distribution; disconnected	Well developed; disconnected
2	Well developed	+	0	On rim of inferior margin	On rim of ventricular septal defect	Well-developed even distribution	Well developed
3	Well developed	+	0	Close to inferior margin	On rim of ventricular septal defect	Well-developed even distribution	Well developed

+, present; 0, absent.

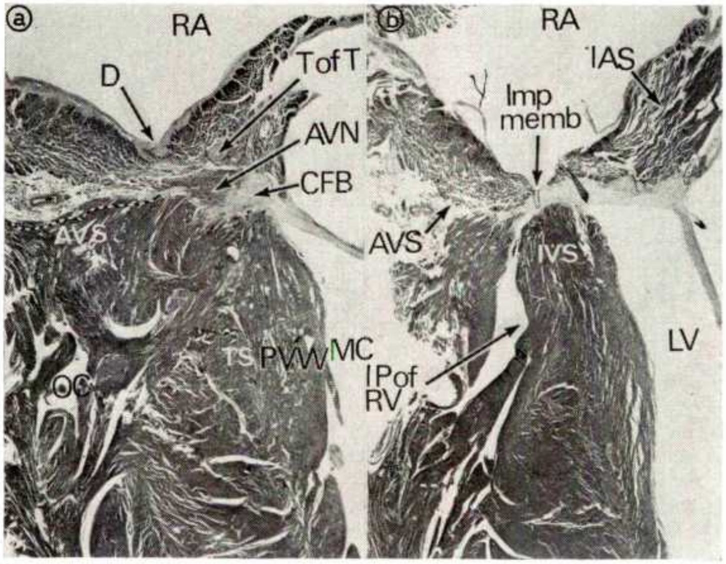

Fig. 4. (*a*). *The histological features in a specimen with 'classical tricuspid atresia'. There is no possibility of a potential connection between the dimple in the floor of the right atrium and the anterior (outlet) chamber of the ventricular mass.* (*b*). *The histological features of case 3. An imperforate membrane is interposed between the right atrial dimple and the hypoplastic inlet portion of the right ventricle.*
RA, right atrium; LV, left ventricle; MC, main chamber; IP of RV, inlet portion of right ventricle; OC, outlet chamber; T of T, tendon of Todaro; AVN, atrioventricular node; CFB, central fibrous body; IVS, interventricular septum; D, dimple; Imp memb, imperforate membrane; AVS, atrioventricular sulcus; PVW, posterior ventricular wall; IAS, interatrial septum.

view, while still agreeing that hearts with left atrioventricular valve atresia ('tricuspid atresia' with L bulboventricular loop) would be examples of the univentricular heart. Our studies unequivocally show that in the 3 cases reported here the right atrium is in potential communication with the anterior chamber. They are not, therefore, univentricular hearts. However, in the majority of cases of right atrioventricular valve atresia, there is no potential connection between the right atrium and the anterior chamber. Indeed the blind right atrium communicates potentially with the main ventricular chamber via the atrioventricular component of the membranous septum (Rosenquist *et al.*, 1970; Anderson *et al.*, 1977). In this situation, our studies show that the anterior chamber has only trabecular and infundibular components and is directly comparable to the anterior rudimentary chamber seen in 'single ventricle with outlet chamber'. These hearts are, therefore, examples of univentricular hearts with absence of the right atrioventricular connection. We know of no evidence to support the view (Bharati and Lev, 1977b) that the atrioventricular orifice may be placed anywhere in this situation by secondary haemodynamic changes after the first 2 months of gestation.

The findings with regard to conducting tissue disposition (Table) are entirely in keeping with these concepts. In the cases presently described, the atrioventricular bundle is related to the inlet septum in a fashion directly comparable to that seen in isolated ventricular septal defect with atrioventricular concordance. In contrast, in examples of 'tricuspid atresia' with absent right atrioventricular connection, the ventricular conducting tissues are arranged as in univentricular hearts of left ventricular type with 2 atrioventricular valves ('single ventricle with outlet chamber') (Dickinson *et al*, 1979).

EMBRYOLOGICAL IMPLICATIONS

In the classical type of 'tricuspid atresia', abnormal development may be explained by failure of lateral expansion of the primitive atrioventricular canal

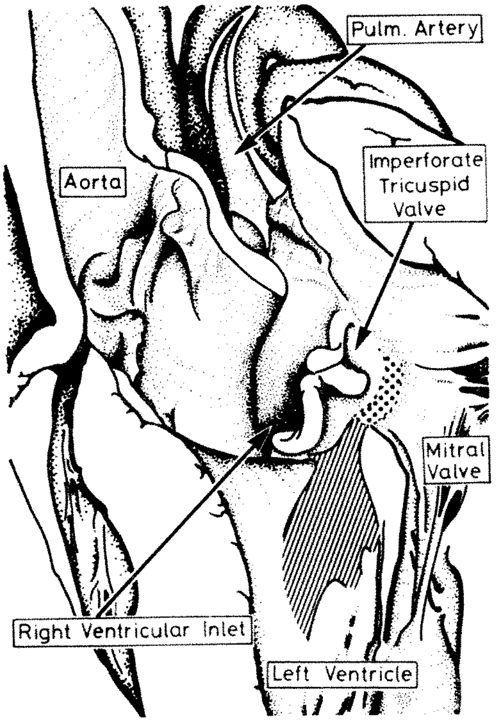

Fig. 5. *Diagram of the conducting tissue in case 2. The orientation of the specimen is as in Fig. 3a. The conducting tissue perforates the central fibrous body medial to the imperforate tricuspid membrane and lies on the posterior inferior rim of the ventricular septal defect.*

with persistence of the trabecular septum in its anterior, embryonic position (Anderson *et al.*, 1977). The embryonic bulbus therefore persists as the rudimentary chamber and the underdeveloped right atrioventricular inlet portion remains within the main ventricular chamber. However, in the present cases, rightward expansion of the atrioventricular canal has proceeded with normal alignment of atria with the two ventricles and development of the posterior inlet septum. Though the right atrioventricular inlet portion has made contact with the bulbus, the tricuspid valve has failed to develop and remains imperforate. The association, in our 3 cases, with left juxtaposition of the atrial appendages, suggests a more complex abnormality of bulboventricular looping than is usually the case in the classical type of 'tricuspid atresia'. Ventriculoarterial discordance, underdevelopment of the right ventricle, and atresia of the right atrioventricular orifice occur with considerable frequency in left juxtaposition of the atrial appendages (Melhuish and Van Praagh, 1968), and it is possible that atrioventricular concordance was present in some of the previously described cases. It is not possible to determine this retrospectively from the published reports, and, as we have shown, histological study is usually necessary to confirm atrioventricular concordance.

SURGICAL IMPLICATIONS

The observation that these cases are anatomically distinct from classical 'tricuspid atresia' is of little clinical importance, since in the described cases the right ventricular inlet component was severely underdeveloped and of little functional significance. The presence of ventriculoarterial discordance would in any case preclude the use of the right ventricle in any surgical repair, direct right atrial to pulmonary artery connection being probably the only radical reconstructive operation feasible.

Nevertheless, it is worth while re-emphasising that some cases of atrioventricular concordance with imperforate tricuspid valve have good sized right ventricles, the imperforate valve exhibiting Ebstein's malformation (Rao *et al.*, 1973). Here the distinction between 'tricuspid atresia' with atrioventricular concordance and 'tricuspid atresia' in a univentricular heart may be of considerable importance as the right ventricle might then be surgically 'salvageable'.

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Double outlet from chambers of left ventricular morphology

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SUMMARY This series of 5 cases with double outlet of morphologically left ventricular chamber includes 4 found during a review of 1700 heart specimens (incidence 0·23%) and 1 found at operation and successfully corrected. Abnormal atrioventricular connection precluding total correction was present in the 4 anatomical cases. Clinical diagnosis may be difficult and it is suggested that axial cineangiography may make anatomical diagnosis easier. Absence of the infundibular septum and aortic laevoposition are frequent. As some cases can be surgically corrected, accurate information is required on the size of the right ventricle, the morphology and function of the atrioventricular valves, the presence, size, and position of the ventricular septal defect, and the degree and type of outflow tract obstruction.

In double outlet left ventricle (DOLV), both great arteries are connected to the left ventricle. If a ventricular septal defect underlies only one of the great arteries, DOLV exists when more than one and a half great arteries arise from the left ventricle (Kirklin, 1973). However, when a doubly committed type of ventricular septal defect is present such a definition should be modified in the sense that more than half of each great artery has to arise directly from the left ventricle (Otero Coto and Quero Jimenez, 1977). Occasionally, the presence of an exactly biventricular origin of a great artery will make its assignment to either ventricle impossible (Brandt *et al.*, 1976).

This anomaly was first reported by Marechal in 1819 (Van Praagh and Weinberg, 1977), and mentioned as a possibility by Rokitansky in 1852. We have found no other published case until 1962 when Fragoyannis and Kardalinos described as DOLV a heart which eventually was shown to have a double outlet 'right' ventricle with atrioventricular discordance and situs solitus. Subsequently DOLV was regarded as an 'embryological impossibility' (Anderson *et al.*, 1974). In 1967 Sakakibara *et al.* reported the first successful repair of a DOLV; surgical experience was further amplified by Pacifico *et al.* (1973). Interest in this entity was further increased by the report by Paul *et al.* (1970) of the first anatomically proven case of DOLV with intact interventricular septum.

Since approximately 75 per cent of all cases of DOLV hitherto reported (Van Praagh and Weinberg, 1977) seem amenable to surgical correction, continued interest in this relatively uncommon lesion is justified.

Subjects

Of the 5 cases of double outlet from a morphologically left ventricular chamber presented in this paper, 4 were identified during a review of 1700 heart specimens with congenital heart malformations (0·23%). Case 5 was diagnosed in the operating room and treated surgically.

CASE 1[1]: VISCERO-ATRIAL SITUS SOLITUS WITH LEFT-SIDED CARDIAC APEX

The right atrium received the coronary sinus and venae cavae, and showed tricuspid atresia with a dimple situated above the main (morphologically left ventricular) chamber. A patent foramen ovale was present. The left atrium received the pulmonary veins and connected with the ventricle through an abnormal atrioventricular valve possessing two leaflets and a large deficiency in the anterior commissure, the commissural tissue being attached by very short chordae tendineae to the ventricular wall. The great arteries arose side by side from this

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[1] Dr Otero-Coto is an Evarts A. Graham Memorial Travelling Fellow of the American Association for Thoracic Surgery.

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[1] Previously reported by Quero Jimenez and Maitre Azcárate (1975).

morphologically left ventricle, with the aorta to the right of the pulmonary artery. A bilateral infundibulum prevented fibrous continuity between semilunar and atrioventricular valves. Laevoposition of the infundibular septum resulted in a malalignment type of ventricular septal defect, limited by the superior border of the muscular interventricular septum and the subaortic free wall. Both semilunar valves were morphologically normal, the pulmonary valve being dilated. The ventricular septal defect communicated with a small cavity, with right ventricular morphology but without valve apparatus or direct connection with any other chamber or vessel. A single coronary artery orifice was present and no delimitant coronary arteries were found. The aortic arch was left-sided and a large persistent ductus arteriosus was present.

CASE 2[1]: SITUS AMBIGUUS WITH ASPLENIA AND RIGHT-SIDED CARDIAC APEX

No interatrial septum was present except for a small anterosuperior remnant (single atrium). There was only one atrioventricular valve of primitive morphology with 4 leaflets opening into a morphologically left ventricular cavity. In the right posterior part of this ventricle a small recess was present, perhaps corresponding to the remnant of the apical recess. Both great arteries arose from the ventricle, being supported by a bilaterally developed infundibulum. The aorta was situated in front and to the left of the pulmonary artery. The aortic arch was right-sided. Mild valvar and subvalvar pulmonary stenosis was present. No coronary sinus was found.

CASE 3: VISCERO-ATRIAL SITUS SOLITUS WITH LEFT-SIDED CARDIAC APEX

A patent, dilated, foramen ovale was present. The atria were morphologically normal and drained through atrioventricular valves of similar size and morphology (each having two leaflets) into a single morphologically left ventricle (Fig. 1). The pulmonary artery and most of the aorta arose from this chamber. There was fibrous continuity between the pulmonary valve and the right atrioventricular valve, but the aortic valve was supported by a well-developed subaortic infundibulum. The small infundibular septum was laevoposed and situated on the roof of the ventricle (Fig. 2); its anterior prolongation formed an abnormal band to the left of the muscular septum. A large ventricular septal defect (3 × 2 cm), limited by the superior border of the muscular septum, the subaortic infundibular free wall, and the anterior ventricular wall, com-

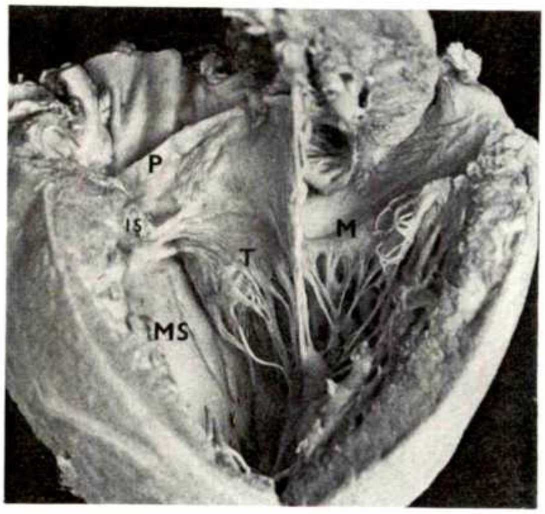

Fig. 1 *Case 3. Inflow tract showing both atrioventricular valves, of similar morphology, draining into the morphologically left ventricular main chamber. The pulmonary valve (P) is in fibrous continuity with the right atrioventricular valve (T). M, left atrioventricular valve; IS, infundibular septum; MS, muscular septum.*

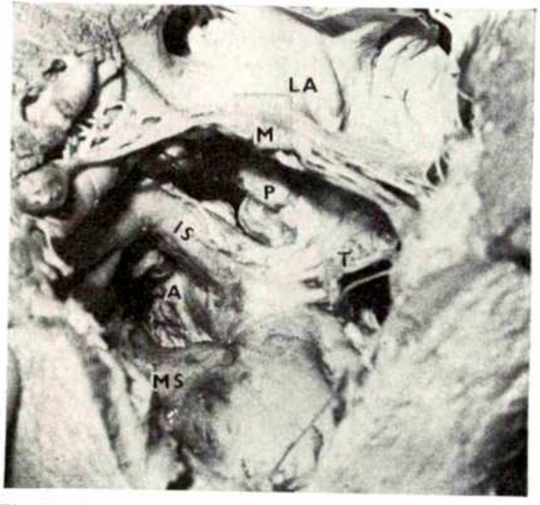

Fig. 2 *Case 3. Outflow tract showing both great arteries connected with the morphologically left ventricular main chamber and separated by the infundibular septum (IS), which is clearly malaligned with the muscular septum (MS). The right atrioventricular valve (T) is shown in fibrous continuity with the pulmonary valve (P) and the left atrioventricular valve (M) has been opened with the left atrium (LA), through an incision in the left lateral border of the heart.*

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[1] Also included in a series of anomalies with aortic laevoposition (Otero Coto *et al.*, 1978).

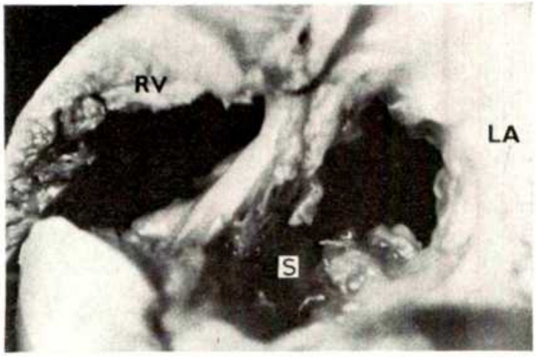

Fig. 3 *Case 4. The straddling left atrioventricular valve is seen with its major part, showing dysplastic changes, entering the left (right-sided) ventricle. LA, left atrium; RV, right (left-sided) ventricle; S, interventricular septum.*

municated with a chamber in which there were no remnants of valve apparatus; this small chamber showed a right ventricular pattern of trabeculation. Both semilunar valves were normal, the aortic valve being anterior to and to the left of the pulmonary valve. Two coronary arteries were present; the right coronary artery crossed the pulmonary outflow tract and its peripheral pattern was bizarre. The aortic arch was left-sided.

CASE 4: ATRIAL SITUS SOLITUS AND LEFT-SIDED CARDIAC APEX

The right atrium, morphologically normal, showed a patent foramen ovale and was connected through a bizarre atrioventricular valve, with 6 well-developed papillary muscles, to a right-sided morphologically left ventricle. The left atrium, morphologically normal, communicated with both ventricular cavities through a straddling left-sided atrioventricular valve, which showed dysplastic changes where it communicated with the left ventricle (without chordae tendineae or papillary muscles) and normal morphology on its right (left-sided) ventricular aspect (Fig. 3). In the left ventricle there was a well-developed posterior muscular column between the atrioventricular valves. Both great arteries arose above the left ventricle; no infundibular septum was present and the aortic valve, directly anterior to the pulmonary valve, was partially related to the right ventricle (Fig. 4). The large ventricular septal defect was limited by the muscular interventricular septum, the right atrioventricular valve, the aortic valve and subaortic infundibular free wall, and the anterior ventricular wall. There were 2 coronary arteries with the usual pattern for corrected transposition. The aortic arch was left-sided.

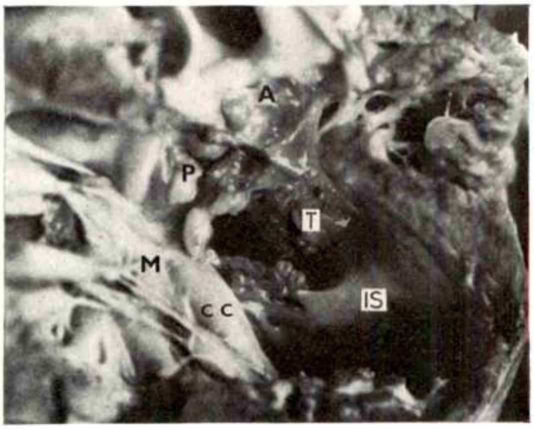

Fig. 4 *Case 4. The morphologically left (right-sided) ventricle has been opened, showing the origin of both great arteries. The left (right-sided) atrioventricular valve (M) is morphologically abnormal, with 6 well-developed papillary muscles. A well-developed posterior muscular column (CC) is placed between the atrioventricular valves. The right (left-sided) atrioventricular valve (T) straddles the posterior part of a ventricular septal defect. The semilunar valves are in fibrous continuity as a result of the absence of the infundibular septum. The pulmonary valve is seen in fibrous continuity with both atrioventricular valves. A, aorta; P, pulmonary valve; IS, interventricular septum.*

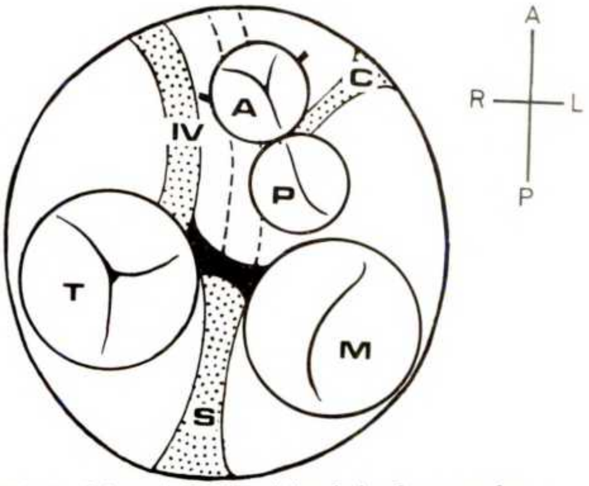

Fig. 5 *Schematic drawing of the relations between valves and septa in case 5, looking towards the base of the ventricles. The position of the muscular interventricular septum in the anterior part is depicted by the dashed lines. T, tricuspid valve; M, mitral valve; A, aortic valve; P, pulmonary valve; S, sinus or inlet septum; IV, infundibulo-ventricular fold; C, infundibular free wall.*

CASE 5: ATRIAL SITUS SOLITUS

The right atrium received 2 venae cavae and the coronary sinus, and communicated through a large ostium secundum atrial septal defect with a morphologically normal left atrium receiving 4 pulmonary veins. Morphologically normal atrioventricular valves established a concordant atrioventricular connection. The right ventricle, of normal size, showed a large abnormal muscle bundle in the superior part and communicated with the left ventricle through a large ventricular septal defect, extending from the atrioventricular valves to the anterior wall. Both great arteries arose from the left ventricle and were related to the ventricular septal defect (doubly-committed type) (Fig. 5). No muscular infundibular septum was present, the semilunar valves being in fibrous continuity. A well-developed conal free wall (infundibulo-ventricular fold) separated the aorta from the tricuspid valve, while the pulmonary valve was in fibrous continuity with the mitral valve. The pulmonary valve was bicuspid and mildly stenotic; there was a fibrous shelf below the pulmonary valve, producing moderate obstruction. Both anterior and posterior descending coronary arteries arose from the right coronary artery (Fig. 6) There was no innominate artery, the right subclavian and common carotid arteries arising independently from the left-sided aortic arch.

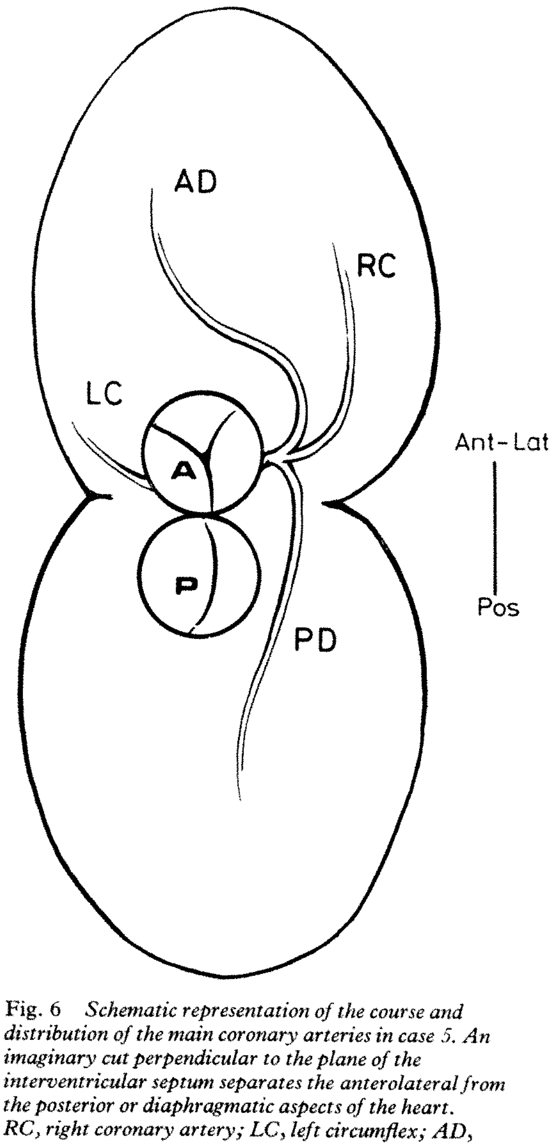

Fig. 6 *Schematic representation of the course and distribution of the main coronary arteries in case 5. An imaginary cut perpendicular to the plane of the interventricular septum separates the anterolateral from the posterior or diaphragmatic aspects of the heart. RC, right coronary artery; LC, left circumflex; AD, anterior descending; PD, posterior descending; A, aorta; P, pulmonary artery.*

Surgical correction was achieved by closing the ventricular septal defect, thus leaving both great arteries connected to the left ventricle, and placing an external valved conduit (Hancock no. 18) between the right ventricle and the pulmonary artery. The pulmonary valve was closed by direct suture. In addition a large atrial septal defect was closed with a patch. The postoperative course was uneventful. Fig. 7 illustrates the view through the tricuspid valve of the ventricular septal defect and the origin of both great arteries. Fig. 8 shows the steps taken in the correction of the malformation.

Discussion

These cases further illustrate the large number of anatomical variations that can occur with double outlet of morphologically left ventricular chamber. The main reported variations relate to the presence or absence and location of the ventricular septal defect or pulmonary stenosis, the infundibular muscular distribution, and the relations of the great arteries. Anomalies of the atrioventricular valves, of the atrioventricular connections, and of the right ventricle or its equivalent are also frequent. Each of the 5 cases presented here had a different type of atrioventricular connection; 2 had a single atrioventricular valve, one with typical mitral morphology, except for the presence of a large deficiency in the anterior commissure, and the other with primitive morphology (this being the only reported case with asplenia to our knowledge). The other 3 cases had 2 atrioventricular valves, but in one both valves opened into the morphologically left ventricle, in another the right (left-sided) atrioventricular valve was straddling the interventricular septum in

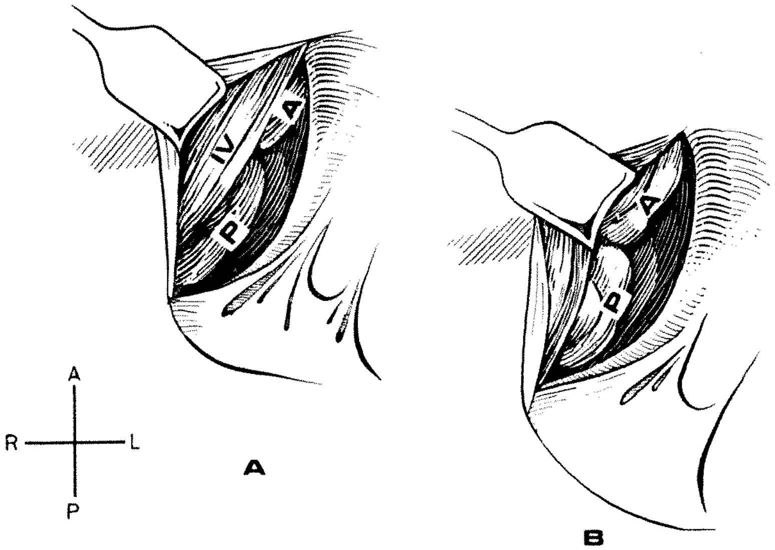

Fig. 7 *Case 5. Initially the right atrium was opened and the anterior leaflet of the tricuspid valve retracted showing (as viewed by the surgeon at operation): (A) the presence of a muscular bundle, the infundibulo-ventricular fold (IV), covering most of the ventricular septal defect, and (B) after retraction of this bundle, the origin of both great arteries to the left of the interventricular septum, both being related to the ventricular septal defect. A, aorta; P, pulmonary artery. Exposure by this route was deemed inadequate and a ventriculotomy was made.*

a case with discordant atrioventricular connection, and in the third case, surgically corrected, both atrioventricular valves connected normally with the appropriate ventricles.

None of the 5 cases was accurately diagnosed before death or operation. The lesion is a rare one and often therefore unsuspected, and angiocardiographic interpretation can be difficult. Selective left ventriculography has been considered (Pacifico *et al.*, 1973) the best way of demonstrating the presence of DOLV, but right ventriculography can also be of value in some cases (Brandt *et al.*, 1976). In our view, a number of projections, including those selective for the anterior part of the interventricular septum (hepatoclavicular technique and long axis oblique view of Bargeron *et al.*, 1977), may be necessary, particularly in cases of transposition of the great arteries with subaortic ventricular septal defect (Quero Jimenez and Perez Martinez, 1974) or anatomically corrected malposition (Otero Coto, 1977).

Perhaps the greatest difficulty in the diagnosis of DOLV lies in accurately applying the 50 per cent rule. Cases with absence of the infundibular septum are particularly difficult to classify. With normally related great arteries the outflow tracts cross and a large deficiency of the septum below one or both

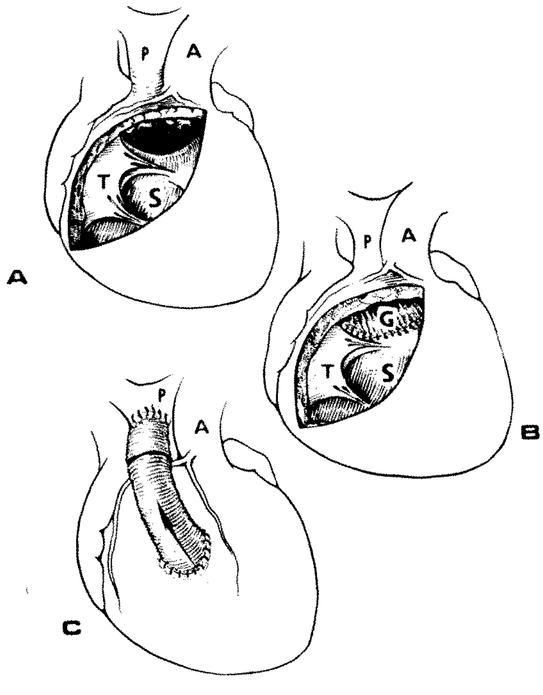

Fig. 8 *Diagrams illustrating the steps followed in the correction. (A) Right ventriculotomy allowed good exposure of the origin of both great arteries to the left of the interventricular septum. (B) After closure of the ventricular septal defect both great arteries connected to the left ventricle. (C) Anatomical continuity between the right ventricle and pulmonary artery was established by interposition of an external valved conduit. T, tricuspid valve, S, interventricular septum; A, aorta; P, pulmonary artery; G, Dacron patch graft used in the closure of the ventricular septal defect.*

great arteries easily creates the appearance of an abnormal connection. Classification is less difficult in cases with discordant ventriculo-arterial connection and anterior aorta, in which the outflow tracts do not cross. In case 5, the initial impression at operation was that the aorta was completely connected to the left ventricle (Fig. 7). However, the relation of the infundibulo-ventricular fold to the muscular interventricular septum (slightly to the right but not completely aligned) proved that a small part of the aorta was above the right ventricle, though more than two-thirds of the (tricuspid) aortic valve was above the left ventricle.

In the absence of atrioventricular discordance, the finding of an anterior descending coronary artery arising from the right coronary artery and leaving both great arteries to its left suggests DOLV. However, this coronary artery pattern is common in cases of anatomically corrected malposition (Otero Coto *et al.*, 1978), in which the aorta is anterior and to the left of the pulmonary artery with ventriculo-arterial concordance, and can occur in other anomalies.

The designation DOLV is not incompatible with a univentricular heart, since the ventriculo-arterial relations and connections are determined by the same rules as in hearts with two well-developed ventricles (Otero Coto, 1977). However, we prefer the designation double outlet of chamber of left ventricular morphology when considering univentricular hearts. Since in univentricular hearts with double outlet left (main chamber) ventricle, neither great artery arises from the blind outlet chamber, we prefer to describe this as a 'trabeculated pouch' (Shinebourne *et al.*, 1978).

DOLV (or chamber of left ventricular morphology) with intact septum or with a non-committed ventricular septal defect (thus far not described) might be classified as complete forms, while DOLV with one or both great arteries related to a ventricular septal defect could be considered incomplete or partial forms.

SURGICAL IMPLICATIONS

Correction of DOLV can be accomplished by intraventricular rerouting, provided that both ventricles are of adequate size, that there is no obstruction to the outflow tracts, or that obstruction if present can be surgically relieved, and that the ventricular septal defect is either subpulmonary or doubly-committed and non-restrictive. However, all of these conditions are seldom met and surgical correction must then be achieved by closing the ventricular septal defect, thus leaving both great arteries connected to the left ventricle, and by placing an external valved conduit between the right ventricle and the pulmonary artery.

Because of the high incidence of a coexisting hypoplastic right ventricle or of anomalous atrioventricular connections, many patients with double outlet of morphologically left ventricular chambers are unfortunately at present unsuitable for total correction. Some are candidates for palliative operations and a few may be suitable for a Fontan type of operation, as was done in the patient reported by Sharratt *et al.* (1976).

An accurate assessment of the size of the right ventricle and of the anatomy and function of the atrioventricular valves is indispensable in planning an operation, and other important considerations are the presence, size, and position of the ventricular septal defect and the degree and type of pulmonary and aortic outflow tract obstruction.

EMBRYOPATHOGENESIS

According to Goor *et al.* (1972), the definitive configuration and the type of connection of the outflow tracts of the ventricles results mainly from 3 developmental processes: conotruncal (bulbar) inversion, leftward shift of the conoventricular junction, and absorption of the conus. These processes are not necessarily linked to each other. DOLV would be the result of conotruncal leftward 'overshift' (Goor and Edwards, 1973), and the varied infundibular patterns the result of different degrees of conus absorption, while different degrees of conotruncal inversion (clockwise or counterclockwise) would explain the different relations of the great arteries. The frequent occurrence of hypoplastic right ventricle or univentricular heart in patients with double outlet of a left ventricular chamber suggests that those anomalies are pathogenetically related to DOLV (De la Cruz, 1977). Aortic laevoposition, which is in our experience frequently associated with right ventricular hypoplasia, is relatively more common in double outlet left ventricular chamber than in any other type of ventriculo-arterial connection with concordant atrioventricular connection (Otero Coto, 1977).

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Two-chambered right ventricle: simulating two-chambered left ventricle

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SUMMARY Two cases are described of a most unusual variant of two-chambered right ventricle. In both the ventricular septal defect was between the distal chamber of the right ventricle and the left ventricle. However the extensive dividing 'septum' between proximal and distal parts of the right ventricle converted the latter, haemodynamically, into part of the left ventricle. In the first case the distal chamber supported the aorta in the left anterior position, the pulmonary artery arising from the proximal part of the right ventricle. In the second the pulmonary artery arose from the distal chamber and the aorta from the proximal chamber. Though in both the ventriculoarterial connection was double outlet right ventricle, functionally there was arterial concordance in case 1 and discordance in case 2. A further disconcerting feature was the resemblance of the distal right ventricular chamber to the rudimentary chamber of a univentricular heart of left ventricular type.

It is well known that a morphologically right ventricle can become divided by muscular bands into two discrete chambers. The distal part of the right ventricle may then resemble the rudimentary chamber seen in a univentricular heart of left ventricular type (Anderson *et al.*, 1976). Though usually associated with concordant ventriculoarterial connections, such a two-chambered right ventricle might exist with double outlet right ventricle. The distal subarterial part of such a two-chambered right ventricle could then communicate via a ventricular septal defect with the left ventricle. If the right ventricular 'septum' were sufficiently well developed, its distal chamber could haemodynamically and functionally become part of the left ventricle. Though we are unaware of previous descriptions of such malformations, we have now encountered two examples, which both give the appearance of 'two-chambered left ventricles'.

Case 1

A male infant (birthweight 3·6 kg) was referred at the age of 3 months to another hospital, where a diagnosis of ventricular septal defect was made. Despite treatment he did not gain weight and had several severe upper respiratory tract infections. At 5 months of age he was admitted to the Children's Hospital, University of Graz.

On examination his weight was below the third centile and he was acyanotic. Pulses were normal and systolic blood pressure was 100 mmHg. The liver was palpable 3 cm below the right costal margin. The second component of the second heart sound was accentuated and there was a grade 4/6 pansystolic murmur at the third left intercostal space. Chest *x*-ray film showed situs solitus with laevocardia; there was cardiomegaly with straight upper left cardiac border, and pulmonary plethora. The electrocardiogram showed sinus rhythm, a mean frontal QRS axis of +110°, right ventricular hypertrophy, and a shortened QT interval, the latter being attributed to digoxin therapy. Q waves were not seen in the praecordial leads.

At cardiac catheterisation, two ventricles and both great arteries were entered, the ascending aorta via a ventricular septal defect, and the left ventricle via right atrium, patent foramen ovale, and left atrium. The right ventricular (60/3 mmHg) and pulmonary artery pressures (45/15 mmHg) were raised but were below systemic level. The systolic pressure in the ascending aorta was the same as in

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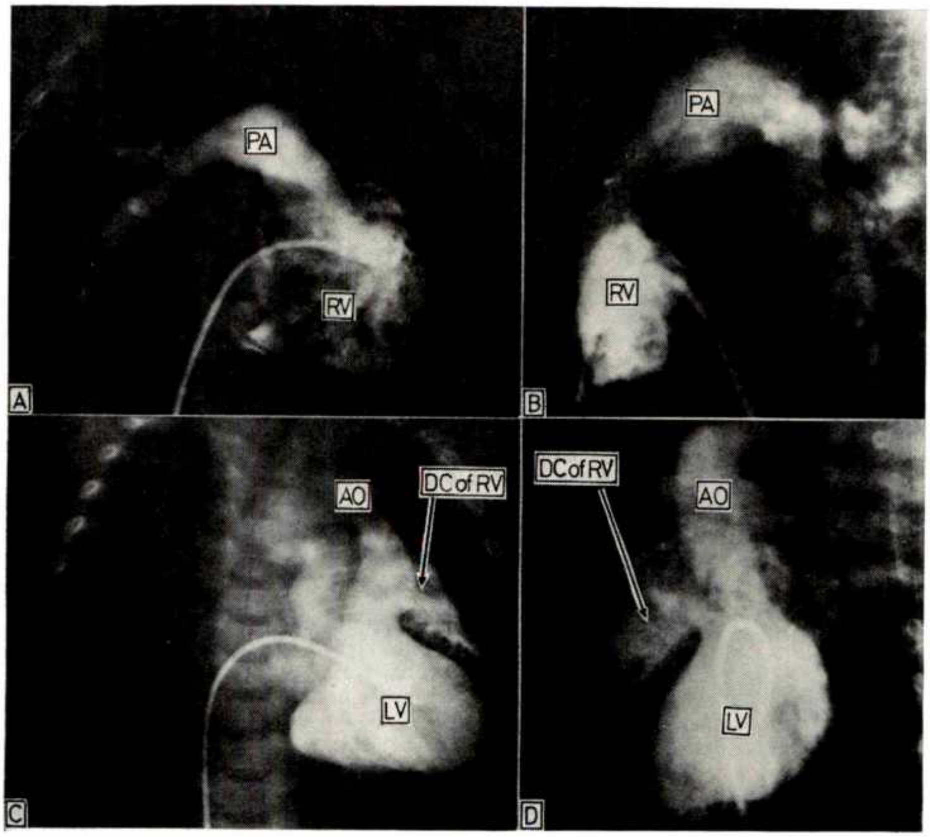

Fig. 1 *Case 1. Angiocardiograms. Fig. 1A shows an injection into the morphologically right ventricle in the frontal projection; Fig. 1B is the same injection in the lateral projection. The right ventricle (RV) gives rise to the pulmonary artery (PA). Fig. 1C and 1D show a left ventricular injection in frontal (C) and lateral (D) projections. The left ventricle (LV) is in continuity with the distal chamber of a two-chambered right ventricle (DC of RV), and the aorta (AO) overrides the septum between the chambers.*

the left ventricle (94 mmHg). Oximetry showed a large left-to-right shunt and a small right-to-left shunt at ventricular level. The $\dot{Q}p/\dot{Q}s$ ratio was 2·4:1.

Subsequent catheterisation 12 months later, performed because of recurrent chest infections and persistent cardiomegaly, showed almost normal right ventricular (35/5 mmHg) and pulmonary artery (35/12 mmHg) pressures but the left-to-right shunt had decreased, with a $\dot{Q}p/\dot{Q}s$ ratio of 1·7:1. At this time there were no signs of cardiac failure and the chest infections were found to be related to hypogammaglobulinaemia.

The angiocardiographic features from the two studies have been combined for ease of presentation.

The presence of situs solitus was confirmed, the catheter entering a morphologically right atrium through a right-sided inferior vena cava. A right-sided anterior ventricle was entered from the right atrium and this chamber was triangular and coarsely trabeculated (Fig. 1A). The pulmonary artery arose from this chamber and there was infundibular tissue between the tricuspid and pulmonary valves (Fig. 1B). A left-sided and posterior ventricular chamber was entered via the left atrium and left-sided atrioventricular valve. This chamber was smooth-walled and ovoid (Fig. 1C and 1D). The injection into the left-sided ventricular chamber also disclosed the presence of a third discrete chamber within the ventricular mass (Fig. 1C). This chamber gave rise to a left-sided anterior aorta, with aortic valve at the same level as the pulmonary valve and separated by infundibular tissue from both atrioventricular valves (Fig. 1C). A selective

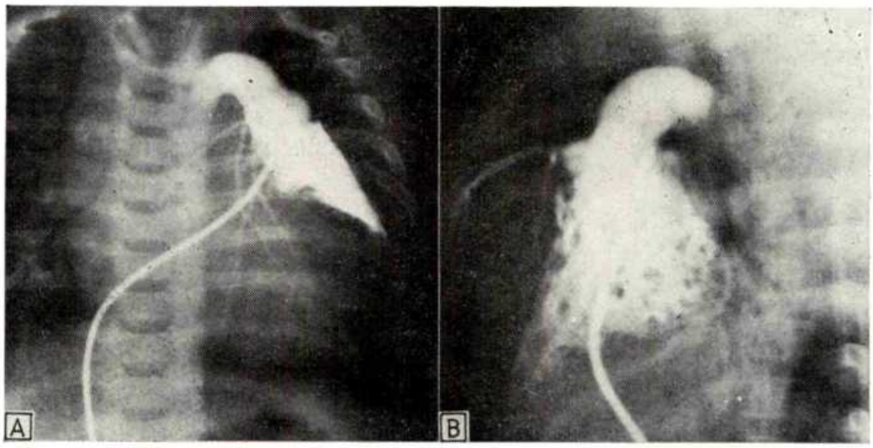

Fig. 2 *Case 1. Angiocardiogram with selective injection into the distal chamber of the right ventricle, viewed in the frontal (Fig. 2A) and lateral (Fig. 2B) projections. The chamber has a trabecular zone with right ventricular characteristics and supports part of the aorta.*

injection into this chamber (Fig. 2A and 2B) showed that it possessed a coarse trabecular zone and did indeed give rise to the aorta.

The angiocardiograms were interpreted as showing the presence of situs solitus, atrioventricular concordance, with double outlet from the right ventricle. The third chamber was interpreted as being part of the morphologically right ventricle that had become sequestered in such a way as to communicate mainly with the left ventricle. There was a subaortic ventricular septal defect between the two ventricles and the aorta was left-sided. There was a bilateral infundibulum.

Case 2

This baby girl was admitted to the Royal Liverpool Children's Hospital at the age of 8 days with a history of cyanosis and dyspnoea from the second day of life. On examination she was found to be in cardiac failure with moderate cyanosis. There were no cardiac murmurs. The chest *x*-ray film showed cardiomegaly, a narrow pedicle, and pulmonary plethora. The electrocardiogram showed sinus rhythm with left ventricular preponderance abnormal for age. Angiocardiograms were interpreted as showing complete transposition with ventricular septal defect and overriding of the pulmonary artery. A balloon atrial septostomy was performed, after which progress was initially satisfactory. However the infant then deteriorated rapidly and died at the age of 2½ weeks.

At necropsy the aorta and pulmonary artery were side by side, with pulmonary artery much larger than aorta (Fig. 3A). There was isthmal hypoplasia. An initial segmental diagnosis was made of situs solitus, atrioventricular concordance, and ventriculo-arterial discordance (complete transposition), with the aorta rising from the morphologically right ventricle (Fig. 3B) and the pulmonary artery from the left ventricle (Fig 3D) overriding the ventricular septal defect. Further examination, however, showed that though an interventricular septum was present to the right of the pulmonary artery, the anterior descending branch of the left coronary artery was to the left of the pulmonary artery running in the interventricular groove. Dissection in the ventricular wall beneath the pulmonary artery then disclosed the presence of a third chamber in the ventricular mass (Fig. 3C). This chamber had the trabecular characteristics of the right ventricle, was separated by the infundibular septum and apical trabeculae from the rest of the right ventricle, and from the left ventricle by the anterior trabecular septum reinforced by the trabecula septomarginalis. This subpulmonary chamber was in free communication with the left ventricle via the subpulmonary ventricular septal defect. In contrast, it was almost completely separated from the proximal part of the right ventricle, only a probe patent passage existing between the two parts of the morphologically right ventricle. The pulmonary valve was separated from the mitral valve by the ventriculo-infundibular fold, which was partially attenuated to permit minimal pulmonary mitral fibrous continuity.

The final segmental diagnosis was situs solitus, atrioventricular concordance, and double outlet right ventricle with subpulmonary ventricular septal

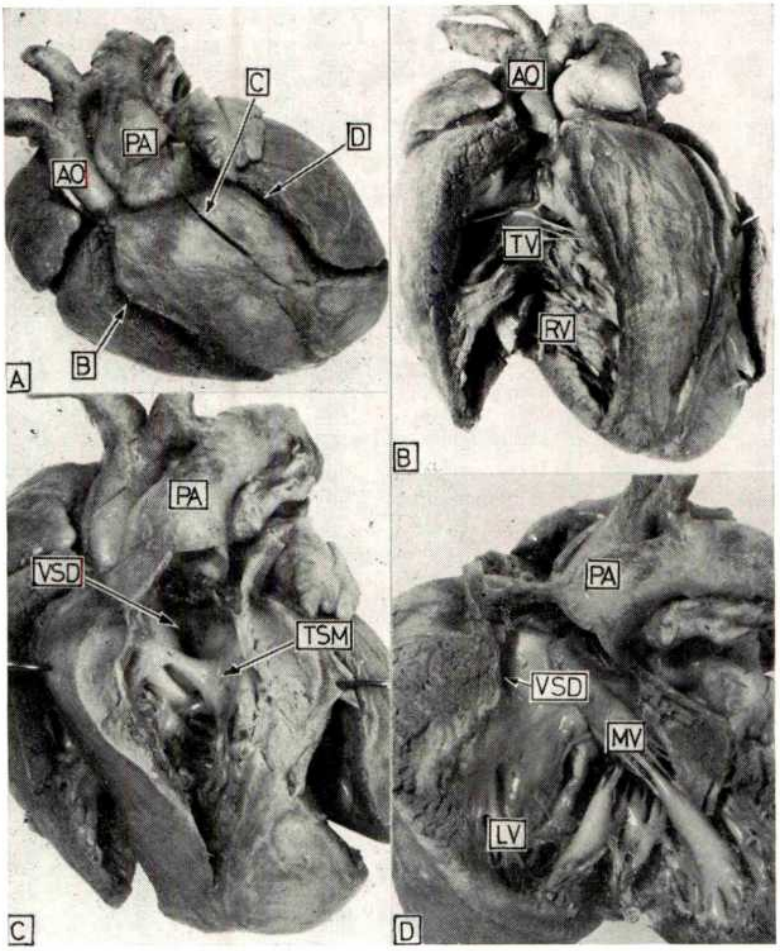

Fig. 3 *Case 2. Photographs of the necropsy specimen. Fig. 3A shows the anterior view of the heart, with the aorta (AO) and pulmonary artery side-by-side. Fig. 3B, 3C, and 3D show the chambers of the heart, viewed through cuts B, C, and D in Fig. 3A. Fig. 3B shows the proximal chamber of the right ventricle (RV), which receives the tricuspid valve (TV) and gives rise to the aorta (AO). Fig. 3C shows the distal chamber of the right ventricle, separated by an almost complete muscular partition from the proximal chamber but in free communication with the left ventricle through the subpulmonary ventricular septal defect (VSD). Note the trabecula septomarginalis (TSM) which forms the lower rim of the defect. Fig. 3D shows the left ventricle (LV), which receives the mitral valve (MV) and supports part of the pulmonary artery (PA), which overrides the defect in the septum (VSD) between the left ventricle and the distal chamber of the right ventricle.*

defect, the important additional anomaly being a two-chambered right ventricle with the distal chamber in free communication with the left ventricle.

Discussion

These cases are of considerable interest in that they possess two ventricles, but also an additional chamber within the ventricular mass, possessing both infundibular and trabecular portions. In this respect, the third chamber is analogous with the rudimentary chamber often seen in univentricular heart of left ventricular type. However, in these hearts there is no question that two ventricles are present, each having an inlet portion containing an atrioventricular valve and a trabecular zone (Tynan *et al.*, 1979). Thus while univentricular hearts can exist without rudimentary chambers, so can rudimentary chambers exist in the presence of biventricular hearts. This is an important consideration, since the angiocardiographic features of case 1 (Fig. 2) were so reminiscent of the outlet chamber of a univentricular heart of left ventricular type that this was the initial diagnosis. Segmental analysis, however, showed that this was not the case, discrete right and left ventricles being unequivocally present. Our proposed explanation for this is that part of the trabecular zone of the morphologically right ventricle had become sequestered by excessive development of the infundibular septum and trabecula septomarginalis in a heart which otherwise consisted of double outlet right ventricle with left-sided aorta and subaortic ventricular septal defect. The morphological findings in case 2 add strong support to this theory.

In this second case, there is little doubt that part of the right ventricle has effectively been incorporated into the morphologically left ventricle by overgrowth of the infundibular septum and its fusion with apical right ventricular trabeculae. Thus, this case is comparable to a double outlet right ventricle with right-sided aorta and subpulmonary ventricular septal defect (Taussig-Bing malformation) in which the right ventricle has become two-chambered and the distal chamber communicates via the ventricular septal defect with the left ventricle. Two-chambered right ventricles are more usually found with concordant ventriculoarterial connections than with double outlet ventricles. Such two-chambered right ventricles, however, are frequent in Fallot's tetralogy (Rowland *et al.*, 1975), and, since there is a spectrum of malformed hearts between the tetralogy of Fallot and double outlet right ventricle (Goor and Edwards, 1973; Anderson *et al.*, 1974), it is not unreasonable to expect that such two-chambered right ventricles should also exist with double outlet from the right ventricle. The two cases described here attest to this possibility. However, to the best of our knowledge they are unique, since the presence of the ventricular septal defect between the left ventricle and the distal chamber of the right ventricle functionally incorporated the distal chamber as part of the *left* ventricle. Thus, though there is no doubt that morphologically the hearts are two-chambered *right* ventricles, haemodynamically they represent two-chambered left ventricles, as in both cases the rudimentary chamber was at the same pressure as the morphologically left ventricle. Furthermore, because part of the right ventricle is sequestered the arterial connection of double outlet right ventricle becomes effectively converted in case 1 to arterial concordance and in case 2 to arterial discordance.

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Left and right ventricular systolic time intervals in the newborn[1]

Usefulness and limitation in distinguishing respiratory disease from transposition of the great arteries

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SUMMARY To determine their usefulness in the evaluation of the cyanotic newborn, left and right ventricular systolic time intervals were determined by echocardiography in 67 neonates; 21 were normal, 25 had neonatal respiratory disease, and 21 had dextro-transposition of the great arteries. The time intervals were measured from high-speed recordings of aortic and pulmonary valve motion.

In normal newborns, the right ventricular pre-ejection period tended to be shorter than the left ventricular pre-ejection period while right ventricular ejection time was longer than that of the left ventricle. The ratio of right ventricular pre-ejection period/ejection time was lower than the ratio of these intervals for the left ventricle in 15 of 21 infants (mean 0·33 ± 0·05 SD compared to 0·39 ± 0·06, $P < 0·001$). In patients with respiratory disease, the ratio of right ventricular pre-ejection period/ejection time was increased, primarily because of prolongation of the pre-ejection period. As a result, the ratio of right ventricular pre-ejection period/ejection time was greater than the left ventricular ratio in 15 of 25 patients and the ratios were equal in 8 (mean 0·44 ± 0·11 vs 0·38 ± 0·08, $P < 0·005$). Likewise, in infants with transposition of the great arteries, right ventricular pre-ejection period/ejection time was greater than left ventricular pre-ejection period/ejection time (0·42 ± 0·10 vs 0·26 ± 0·06, $P < 0·001$), and the lowest values of left ventricular pre-ejection period/ejection time were recorded in this group.

The pulmonary valve closed later than the aortic valve in 46 (70%) of the subjects studied; simultaneous semilunar valve closure occurred in 19 (29%), and in 1 subject with respiratory disease the pulmonary valve closed before the aortic valve.

Thus, the ratio of right ventricular pre-ejection period/ejection time was greater than the left ventricular ratio in both neonatal respiratory disease and transposition of the great arteries. A very low left ventricular ratio (less than 0·25) and delayed closure of the posterior semilunar valve suggest the latter diagnosis.

The measurement of systolic time intervals has been widely used as a non-invasive method of studying cardiac function. Most studies have focused on assessment of left ventricular performance, since the left ventricular systolic time intervals can be readily determined from simultaneous recordings of the electrocardiogram, the indirect carotid pulse tracing, and the phonocardiogram (Weissler *et al.*, 1969, 1972). There have been relatively few studies of right ventricular systolic time intervals (Leighton *et al.*, 1971; Curtiss *et al.*, 1976), primarily because of the difficulty in timing right ventricular events by non-invasive techniques. With the development of echocardiography, it has become possible to measure the systolic time intervals of both the left ventricle and the right ventricle (Hirschfeld *et al.*,

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1975a; Mills *et al.*, 1975; Riggs *et al.*, 1977a, b). Alterations of the systolic time intervals have been shown in patients with pulmonary hypertension (Hirschfeld *et al.*, 1975b; Curtiss *et al.*, 1976) and in patients with transposition of the great arteries (Hirschfeld*et al.*, 1975a).

Clinical differentiation of transposition of the great arteries from respiratory disease may be difficult in the newborn, and a non-invasive method of making the distinction is clearly desirable. Neonates with transposition of the great arteries require prompt catheterisation and are often dramatically improved by Rashkind balloon atrial septostomy (Rashkind and Miller, 1966; Mullins *et al.*, 1972; Neches *et al.*, 1972). Catheterisation of the seriously ill newborn entails considerable risk, however, and obviously should be avoided in the infant with primary respiratory disease.

In the present study, echocardiography was used to measure right and left ventricular systolic time intervals in normal newborns. The results were compared with similar data from neonates with either respiratory disease or transposition of the great arteries to determine the usefulness of this technique in the evaluation of the cyanotic newborn.

Subjects and methods

Echocardiograms were obtained from 67 neonates. The first group consisted of 21 normal newborn infants. They were between 15 and 40 hours of age at the time of study and had no heart disease as judged by physical examination. Informed consent was obtained from the parents and the primary physician before study.

The second group consisted of 25 full-term newborns with respiratory disease. Echocardiograms were performed between 12 and 48 hours after birth. Each patient had cyanosis, clinical evidence of respiratory distress, and arterial blood oxygen concentration below the expected value for the inspired oxygen concentration. The pathogenesis of the respiratory disease frequently was unknown at the time of study and cyanotic congenital heart disease was often an initial diagnostic consideration. However, the final diagnosis was hyaline membrane disease in 5, transient tachypnoea of the newborn (Avery *et al.*, 1966) in 5, persistent fetal circulation (Gersony *et al.*, 1969) in 9, pneumonia in 5, and bilateral choanal atresia in 1.

The third group consisted of 21 patients with dextro-transposition of the great arteries. They ranged in age from 1 day to 6 weeks; 15 were under 1 week of age. The diagnosis was confirmed by cardiac catheterisation and in each patient balloon atrial septostomy was performed. Nine patients had uncomplicated transposition of the great arteries, 7 had an associated ventricular septal defect without pulmonary stenosis, and 3 had ventricular septal defect and pulmonary stenosis. A persistent ductus arteriosus was shown by angiography in 8 of these patients and coarctation of the aorta was present in 2. The incidence of pulmonary stenosis may be underestimated since we avoid repeated attempts to catheterise the pulmonary artery in neonates with transposition of the great arteries (Mullins *et al.*, 1972). The pulmonary artery was entered in only 8 patients, 7 via a ventricular septal defect and 1 via a persistent ductus arteriosus.

Echocardiograms were obtained with a Hoffrel model 101 Ultrasonoscope interfaced to a Honeywell model 1856 strip chart recorder. The left ventricular and right ventricular systolic time

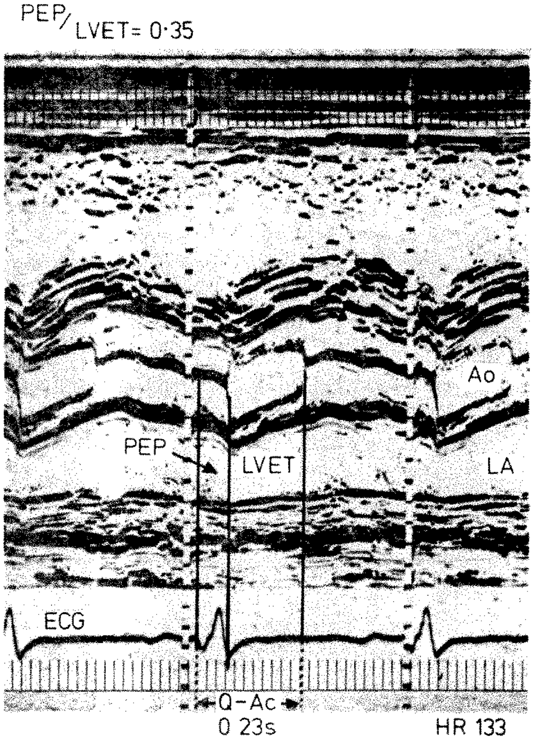

Fig. 1 *Recording of aortic valve motion in a newborn with respiratory disease, illustrating the method for measuring left ventricular systolic time intervals from the echocardiogram. The ratio PEP/LVET was 0·35, and aortic valve closure (Ac) occurred 0·23 s after the onset of the QRS complex of the electrocardiogram (ECG). Time lines are 0·02 s, paper speed 100 mm/s. PEP, pre-ejection period; LVET, left ventricular ejection time; Ao, aorta; LA, left atrium; HR, heart rate.*

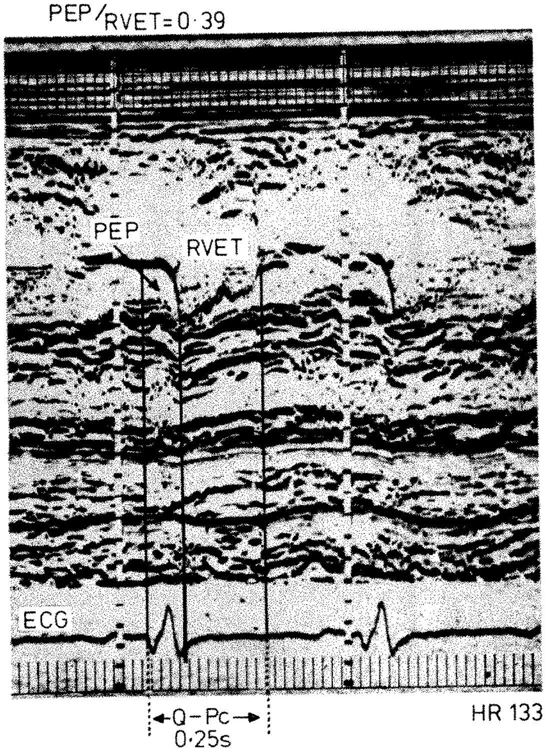

Fig. 2 *Recording of pulmonary valve motion (same patient as Fig. 1) showing method by which right ventricular systolic time intervals were determined. The ratio PEP/RVET is 0·39, and pulmonary valve closure (Pc) occurs 0·25 s after the onset of the QRS complex. PEP, right ventricular pre-ejection period; VET, right ventricular ejection time; HR, heart rate.*

intervals were measured from recordings of aortic and pulmonary valve motion at 100 mm/second paper speed, using the technique described by Hirschfeld *et al.* (1975a) (Fig. 1 and 2). In patients with transposition of the great arteries, left ventricular systolic time intervals were determined from the pulmonary valve recording and right ventricular intervals from the aortic valve recording. For each ventricle the pre-ejection period was measured from the onset of the QRS complex of the electrocardiogram to the point of opening of the corresponding semilunar valve. Left and right ventricular ejection times were measured from semilunar valve opening to closing. The timing of semilunar valve closure was determined by measuring the interval from the onset of the QRS complex of the electrocardiogram to the time of aortic and pulmonary valve closure (Q-Ac and Q-Pc). All measurements were rounded off to the nearest 0·005 second.

Systolic time intervals, particularly those of the right ventricle, are known to be influenced by respiration. Since the phase of the respiratory cycle could not be controlled or recorded during the study, the following method was used to minimise the effects of respiration: (1) systolic time intervals were measured only from records in which each of the semilunar valves was recorded at the same heart rate, and (2) of the cycles recorded at this rate, those with the shortest ejection time were chosen for analysis.

The heart rates of infants with respiratory disease (mean 144 ± 18 SD) and transposition of the great arteries (149 ± 20) were significantly higher than those of the normal newborns (130 ± 12, P < 0·005). Previous studies have shown that the ejection time (Weissler *et al.*, 1969; Leighton *et al.*, 1971; Weissler *et al.*, 1972) and, to a lesser extent, the pre-ejection period (Golde and Bursten, 1970; Leighton *et al.*, 1971; Spitaels *et al.*, 1974; Hirschfeld *et al.*, 1975b) are inversely related to heart rate. Therefore, in the subsequent analysis, the absolute values of the right or left ventricular systolic time intervals have been compared only with those of the other ventricle of the same patient. Since the ratio of pre-ejection period/ejection time is relatively independent of heart rate (Spitaels *et al.*, 1974; Hirschfeld *et al.*, 1975b), it has been used for intergroup comparisons.

Student's t test was used to compare the data from the 3 groups of subjects and the paired t test was used for comparison of the 2 ventricles within each group.

Results

NORMAL NEWBORNS

In 11 of the 21 normal infants, right ventricular pre-ejection period was shorter than left ventricular pre-ejection period; in 4 infants the right and left ventricular pre-ejection periods were equal, and in 6 the right ventricular pre-ejection period was longer. The mean right ventricular pre-ejection period was 0·06 second, compared with the mean left ventricular pre-ejection period of 0·07 second. Right ventricular ejection time was longer than left ventricular ejection time in 19 of 21 subjects and ejection times of the 2 ventricles were equal in 2 (Table 1a).

The shorter pre-ejection period and longer ejection time of the right ventricle resulted in a mean ratio of right ventricular pre-ejection period/ejection time which was significantly lower than the left ventricular ratio (0·33 ± 0·05 SD vs 0·39 ± 0·06, P < 0·001) (Fig. 3). However, in 4 infants (cases 4, 6, 13, and 15) a long right ventricular pre-

Table 1a *Left and right ventricular systolic time intervals: normal newborns*

No.	*HR*	*Left ventricle*			*Right ventricle*			*Q-Ac*	*Q-Pc*
		LPEP	*LVET*	*LPEP/LVET*	*RPEP*	*RVET*	*RPEP/RVET*		
1	125	0·09	0·16	0·56	0·08	0·19	0·42	0·25	0·27
2	100	0·08	0·19	0·42	0·06	0·22	0·27	0·27	0·28
3	140	0·075	0·17	0·44	0·06	0·20	0·30	0·245	0·26
4	133	0·07	0·175	0·40	0·08	0·18	0·44	0·24	0·25
5	110	0·07	0·205	0·34	0·06	0·225	0·27	0·275	0·285
6	133	0·65	0·185	0·35	0·08	0·19	0·42	0·25	0·27
7	118	0·06	0·20	0·30	0·065	0·215	0·30	0·26	0·28
8	133	0·07	0·18	0·39	0·07	0·195	0·36	0·25	0·265
9	136	0·065	0·175	0·37	0·065	0·20	0·32	0·24	0·265
10	133	0·06	0·18	0·33	0·06	0·19	0·32	0·24	0·25
11	133	0·07	0·17	0·40	0·06	0·19	0·31	0·24	0·25
12	110	0·07	0·22	0·32	0·07	0·22	0·32	0·29	0·29
13	150	0·06	0·19	0·32	0·07	0·19	0·37	0·25	0·26
14	130	0·07	0·18	0·39	0·06	0·19	0·32	0·25	0·25
15	136	0·06	0·18	0·33	0·065	0·185	0·35	0·24	0·25
16	120	0·07	0·165	0·42	0·065	0·195	0·34	0·235	0·26
17	125	0·06	0·18	0·33	0·05	0·20	0·25	0·24	0·25
18	140	0·07	0·18	0·39	0·065	0·20	0·32	0·25	0·265
19	133	0·065	0·18	0·36	0·06	0·20	0·30	0·245	0·26
20	130	0·085	0·17	0·50	0·06	0·20	0·30	0·255	0·26
21	120	0·085	0·17	0·45	0·07	0·22	0·32	0·255	0·29
Mean	130	0·07	0·18	0·39	0·06	0·20	0·33	0·25	0·27
SD	12	0·009	0·01	0·06	0·008	0·01	0·05	0·01	0·01

HR, heart rate (beats/minute); LPEP, left ventricular pre-ejection period; LVET, left ventricular ejection time; RPEP, right ventricular pre-ejection period; RVET, right ventricular ejection time; Q-Ac and Q-Pc, interval from onset of QRS complex of electrocardiogram to aortic and pulmonary valve closure, respectively.

ejection period resulted in a mean ratio of pre-ejection period/ejection time greater than that of the left ventricle. The raised right ventricular ratio of these infants was not age-related; their age range of 16 to 38 hours was similar to that of the other normal infants.

Table 1b *Left and right ventricular systolic time intervals: neonatal respiratory disease*

No.	*Aetiology*	*HR*	*Left ventricle*			*Right ventricle*			*Q-Ac*	*Q-Pc*
			LPEP	*LVET*	*LPEP/LVET*	*RPEP*	*RVET*	*RPEP/RVET*		
1	HMD	143	0·075	0·16	0·47	0·085	0·16	0·53	0·235	0·245
2	HMD	160	0·07	0·135	0·52	0·09	0·135	0·66	0·205	0·225
3	HMD	156	0·07	0·15	0·47	0·07	0·15	0·47	0·22	0·22
4	HMD	140	0·065	0·16	0·40	0·06	0·18	0·33	0·225	0·24
5	HMD	145	0·07	0·14	0·50	0·07	0·14	0·50	0·21	0·21
6	PFC	127	0·075	0·17	0·44	0·085	0·175	0·48	0·245	0·26
7	PFC	136	0·065	0·175	0·37	0·075	0·175	0·43	0·24	0·25
8	PFC	157	0·06	0·16	0·38	0·08	0·15	0·53	0·22	0·23
9	PFC	86	0·065	0·195	0·33	0·075	0·22	0·33	0·26	0·295
10	PFC	136	0·055	0·15	0·37	0·06	0·16	0·375	0·205	0·22
11	PFC	150	0·065	0·165	0·39	0·75	0·155	0·48	0·23	0·23
12	PFC	157	0·04	0·16	0·25	0·04	0·16	0·29	0·20	0·20
13	PFC	150	0·07	0·19	0·38	0·10	0·17	0·59	0·26	0·27
14	PFC	133	0·07	0·17	0·41	0·07	0·18	0·39	0·24	0·25
15	TTN	144	0·08	0·20	0·40	0·11	0·17	0·65	0·28	0·28
16	TTN	120	0·055	0·20	0·275	0·07	0·205	0·34	0·255	0·275
17	TTN	165	0·045	0·14	0·32	0·065	0·14	0·46	0·185	0·205
18	TTN	145	0·065	0·19	0·34	0·075	0·195	0·38	0·225	0·27
19	TTN	150	0·065	0·20	0·32	0·08	0·17	0·47	0·265	0·25
20	PN	170	0·06	0·14	0·43	0·06	0·14	0·43	0·20	0·20
21	PN	133	0·045	0·18	0·25	0·045	0·18	0·25	0·225	0·22
22	PN	165	0·055	0·16	0·34	0·055	0·16	0·34	0·215	0·215
23	PN	157	0·08	0·17	0·47	0·08	0·17	0·47	0·25	0·25
24	PN	120	0·075	0·19	0·39	0·08	0·19	0·42	0·265	0·27
25	CA	160	0·05	0·17	0·29	0·05	0·17	0·29	0·22	0·22
Mean		144	0·06	0·17	0·38	0·07	0·17	0·44	0·23	0·24
SD		18	0·01	0·02	0·08	0·02	0·02	0·11	0·02	0·02

CA, choanal atresia; HMD, hyaline membrane disease; PFC, persistent fetal circulation; PN, pneumonia; TTN, transient tachypnoea of the newborn.
Other abbreviations as in Table 1a.

Table 1c *Left and right ventricular systolic time intervals: transposition of great arteries*

No.	*Associated lesions**	*HR*	*Left ventricle*			*Right ventricle*			*Q-Ac*	*Q-Pc*
			LPEP	*LVET*	*LPEP/LVET*	*RPEP*	*RVET*	*RPEP/RVET*		
1		144	0·05	0·24	0·21	0·07	0·18	0·39	0·25	0·29
2		120	0·06	0·21	0·27	0·10	0·17	0·60	0·27	0·27
3		150	0·045	0·195	0·23	0·06	0·16	0·37	0·22	0·24
4		150	0·05	0·20	0·25	0·065	0·16	0·40	0·225	0·25
5		180	0·04	0·18	0·22	0·07	0·14	0·50	0·21	0·22
6		146	0·03	0·21	0·14	0·06	0·15	0·40	0·21	0·24
7	VSD	135	0·06	0·21	0·21	0·065	0·18	0·35	0·245	0·27
8	VSD	145	0·065	0·18	0·36	0·085	0·14	0·60	0·225	0·26
9	VSD	140	0·04	0·20	0·20					0·24
10	VSD	180	0·05	0·20	0·25	0·065	0·17	0·33	0·235	0·25
11	VSD	120	0·05	0·22	0·23	0·08	0·16	0·50	0·24	0·27
12	VSD	135	0·05	0·20	0·25	0·07	0·18	0·39	0·25	0·25
13	PS	155	0·045	0·24	0·19	0·06	0·16	0·37	0·22	0·28
14	PS	145	0·05	0·20	0·25	0·08	0·17	0·47	0·25	0·25
15	VSD, PS	144	0·04	0·20	0·20	0·06	0·16	0·37	0·24	0·27
16	VSD, PS	145	0·05	0·20	0·25	0·07	0·16	0·43	0·23	0·24
17	VSD, PS	120	0·06	0·20	0·30	0·06	0·18	0·33	0·24	0·26
18	PDA	200	0·035	0·135	0·26	0·05	0·11	0·45	0·16	0·17
19	PDA	170	0·055	0·17	0·32	0·045	0·19	0·23	0·235	0·235
20	PDA, CoA	150	0·045	0·20	0·225	0·065	0·17	0·39	0·235	0·240
21	VSD, PDA, CoA	155	0·07	0·16	0·44	0·08	0·13	0·60	0·21	0·235
Mean		149	0·05	0·05	0·26	0·07	0·16	0·42	0·23	0·25
SD		20	0·01	0·02	0·06	0·01	0·02	0·10	0·02	0·03

CoA, coarctation of aorta; PDA, persistent ductus arteriosus; PS, pulmonary stenosis; VSD, ventricular septal defect.
Other abbreviations as in Table 1a.
*Cases 2, 3, 4, and 14 also had a small, but haemodynamically insignificant PDA shown by angiography.

Aortic valve closure preceded pulmonary valve closure by an average of 0·02 second. In 18 of the 21 normal infants, Q-Ac was at least 0·01 second shorter than Q-Pc at the same heart rate; in 3 infants, these intervals were equal (Table 2).

RESPIRATORY DISEASE

In infants with respiratory disease, the left ventricular pre-ejection period and ejection time were similar to those of the normal subjects (Table 1b and Fig. 3). The right ventricular systolic time intervals were different, however. Though patients with respiratory disease had faster heart rates than the normal infants, right ventricular pre-ejection period was longer (0·07 ± 0·02 vs 0·06 ± 0·01 s, P < 0·05). As a result, the mean ratio of pre-ejection period/ejection time for the right ventricle was greater than that for the left ventricle (0·44 ± 0·11 vs 0·38 ± 0·08 s, P < 0·005). There was no apparent relation between the systolic time intervals and either the type or severity of the respiratory disease.

Table 2 *Timing of semilunar valve closure in the newborn*

	Q-Pc > Q-Ac	*Q-Pc = Q-Ac*	*Q-Pc < Q-Ac*
Normal	18	3	0
RDS	12	12	1
TGA	16	4	0
	46	19	1

Q-Pc, Q-Ac, time from Q wave of electrocardiogram to pulmonary or aortic valve closure, respectively; RDS, respiratory distress syndrome; TGA, transposition of the great arteries.

In 12 of the 25 patients with respiratory disease, aortic valve closure preceded pulmonary valve closure, as in the normal subjects (Table 2). Simultaneous semilunar valve closure was equally common; in 12 patients with respiratory distress syndrome, Q-Ac and Q-Pc were identical. In one patient, the pulmonary valve closed before the aortic valve.

TRANSPOSITION OF GREAT ARTERIES

The left ventricular systolic time intervals were particularly useful in distinguishing transposition from respiratory disease. In patients with transposition, the left ventricular pre-ejection period was shorter than in normals or in patients with respiratory disease, while the left ventricular ejection time was prolonged (Table 1c). The resultant ratio of left ventricular pre-ejection period/ejection time was significantly (P < 0·001) lower in transposition of the great arteries (0·26 ± 0·06) than in the other 2 groups (normals = 0·39 ± 0·06, respiratory disease = 0·38 ± 0·08). In 13 of 21 patients with transposition of the great arteries, the ratio of left ventricular pre-ejection period/ejection time was 0·25 or less; no normal infant and only 4 infants with respiratory disease had a ratio less than 0·30.

The left ventricular pre-ejection period/ejection time ratio was higher in patients with transposition complicated by large ventricular septal defect than

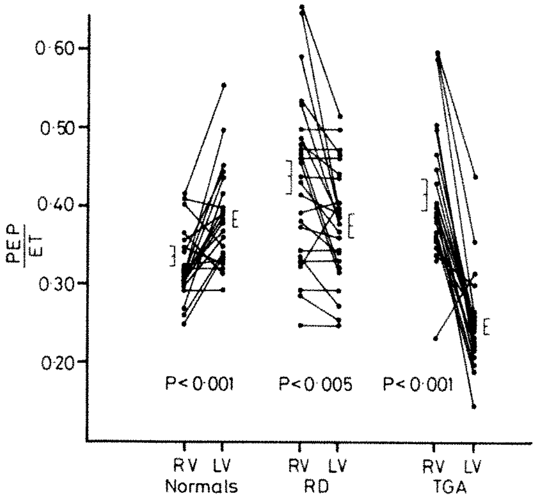

Fig. 3 *Ratio of pre-ejection period (PEP) to ejection time (ET) for the right (RV) and left ventricle (LV) in 3 groups of neonates. In normals, the RV ratio was lower. In infants with respiratory disease (RD) and transposition of the great arteries (TGA), the RV ratio was higher than the LV ratio. Brackets indicate mean ± standard error.*

in those with simple transposition or transposition with pulmonary stenosis (Table 1c). The average ratio for the 7 patients with transposition of the great arteries and ventricular septal defect was 0·28; that for the 5 patients with pulmonary stenosis (3 with and 2 without ventricular septal defect) was 0·24 and that for 6 patients with simple transposition was 0·22.

The right ventricular systolic time intervals in infants with transposition were similar to those of the patients with respiratory disease, and were characterised by a relatively long pre-ejection period and a short ejection time. The ratio of right ventricular pre-ejection period/ejection time was greater than that of the left ventricle in all but 1 patient with transposition of the great arteries, and the mean values for the 2 ventricles provided the most distinct separation of the 3 groups of subjects: right ventricle = 0·42 ± 0·02, left ventricle = 0·26 ± 0·02, $P < 0·001$ (Fig. 3).

The pulmonary valve closed after the aortic valve in 16 of 19 patients with transposition of the great arteries. In the other 3 patients, aortic and pulmonary valve closure was simultaneous (Table 2).

Discussion

In normal subjects, right ventricular ejection begins before and ends after left ventricular ejection (Braunwald *et al.*, 1956). Compared with the left ventricle, the right ventricle is characterised by a short pre-ejection period and a long ejection time (Leighton *et al.*, 1971; Hirschfeld *et al.*, 1975a). In the absence of disorders of myocardial contractility, filling pressure, or conduction, the pressure in the outflow vessel is the major determinant of the systolic time intervals of either ventricle. A rise in the arterial diastolic pressure increases the time required for ventricular pressure to reach arterial pressure and to open the semilunar valve. Though this may, in part, be compensated for by a more rapid rate of rise of ventricular pressure, the net result is usually a prolongation of the pre-ejection period; additionally, arterial hypertension may shorten the ejection time (Curtiss *et al.*, 1976). The result is that the ventricle facing systemic pressure tends to have a higher ratio of pre-ejection period to ejection time than does the ventricle facing pulmonary pressure.

The demonstration that left ventricular and right ventricular systolic time intervals could be measured non-invasively by electrocardiography (Hirschfeld *et al.*, 1975a) suggested that this technique might be of value in the evaluation of the cyanotic newborn. It was unknown whether the rapid heart rates (with shortening of all systolic and diastolic time intervals) and raised pulmonary artery pressure of the newborn would preclude identification of the great arteries by their systolic time intervals.

The ratio of right ventricular pre-ejection period/ejection time was raised in both transposition of the great arteries and respiratory disease. Therefore, the low ratio of left ventricular pre-ejection period/ejection time in transposition was the most useful finding for distinguishing the two conditions. Hirschfeld *et al.* (1975a) showed that in older children with transposition, the left ventricular systolic time intervals were those of a ventricle facing the pulmonary circulation (that is, a short pre-ejection period and long ejection time compared to the other ventricle). The present study confirmed these findings; even in the first week of life, most patients with transposition of the great arteries had left ventricular systolic time intervals characteristic of a 'pulmonary' ventricle. The ratio of left ventricular pre-ejection period/ejection time was lower than that of the right ventricle and the pulmonary valve closed later than the aortic valve.

The relation between the left and right ventricular systolic time intervals in normal newborns in this study is qualitatively similar to that reported in older children and adults (Leighton *et al.*, 1971; Hirschfeld *et al.*, 1975b). Riggs *et al.* (1977a) showed a decline in the ratio of right ventricular pre-ejection period/ejection time within the first 48 hours of life. Most of this decline occurred in the first 12 hours of life; the average value of right ventricular pre-ejection period/ejection time for infants 12 to 48 hours old was 0·315, similar to the value of 0·33 for the 15- to 40-hour old normal subjects in our study. Both studies show that by 12 to 24 hours of age, the right ventricle is characterised by a relatively short pre-ejection period. There were some exceptions, however, consistent with the observation that pulmonary artery pressure is often above normal adult levels in the first week of life (Adams and Lind, 1957; Rowe and James, 1957).

In patients with respiratory disease, the right ventricular systolic time intervals were strikingly altered. The ratio of right ventricular pre-ejection period/ejection time was not only higher than that of normal infants, but was often higher than the ratio of left ventricular pre-ejection period/ejection time. This was primarily because of prolongation of right ventricular pre-ejection period. Previous studies (Halliday *et al.*, 1977; Riggs *et al.*, 1977b) have also indicated a raised ratio of right ventricular pre-ejection period/ejection time in newborns with neonatal respiratory disease. Though pulmonary artery pressure was not measured, we assume that it was high in many of our patients; other studies (Rudolph *et al.*, 1961; Fox *et al.*, 1977) have shown raised pulmonary artery pressure (especially in relation to systemic pressure) in newborns with respiratory disease.

Previous descriptions of the echographic features of transposition of the great arteries have emphasised recognition of the altered spatial relation of the great arteries, either by transducer position and angulation (Gramiak *et al.*, 1973) or by the ability simultaneously to record both semilunar valves from a single transducer position (Dillon *et al.*, 1973). While these findings may suggest the diagnosis of transposition, they are very subjective, and more objective criteria for identifying the great arteries have been sought. Solinger *et al.* (1973, 1974) have emphasised that the pulmonary valve, regardless of its location, closes after the aortic valve. Our results support this finding; if one semilunar valve closed after the other, it was, with one exception, the pulmonary valve. However, in 19 of the infants (29%), including 12 of 25 with respiratory disease, we could find no measurable difference between Q-Ac and Q-Pc.

The values of left and right ventricular systolic time intervals obtained in the present study are consistent with current knowledge of the haemodynamics of the 3 groups of subjects. Since the ratio of right ventricular pre-ejection period/ejection time is higher than that of the left ventricle in both transposition of the great arteries and respiratory disease, it does not appear possible to distinguish these conditions on the basis of this finding. However, transposition should be suspected if (1) the ratio of left ventricular pre-ejection period/ejection time is very low (especially if under 0·25) and (2) the posterior semilunar valve closes after the anterior semilunar valve. Used in this manner, measurement of right ventricular and left ventricular systolic time intervals may be a useful supplement to more subjective M-mode echographic techniques, and to cross-sectional echocardiography (Sahn *et al.*, 1974; Maron *et al.*, 1975; Houston *et al.*, 1978) in the evaluation of the cyanotic newborn.

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Treatment of hypertrophic obstructive cardiomyopathy with verapamil

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SUMMARY Twenty-two patients with hypertrophic obstructive cardiomyopathy were treated with the calcium inhibitor, verapamil, which was administered in a mean oral dose of 480 mg per day. After an average of 15 months of treatment (4 to 24 months), the QRS amplitude in the electrocardiogram was significantly reduced from 4·2 to 3·8 mV. Heart volume calculated from chest *x*-ray films in the supine position decreased significantly from 858 to 766 ml per 1·73 m^2. In 10 patients, follow-up heart catheterisation showed a decrease in left ventricular muscle mass in 7 patients and a slight increase in 3 patients. Coronary artery diameter decreased in 7 patients, increased in 1, and was unchanged in 2. The reduction in coronary artery diameter is considered to be a consequence of a reduced heart muscle mass. From all available clinical data it is concluded that verapamil treatment is superior to beta-blocker therapy.

Hypertrophic obstructive cardiomyopathy (HOCM), first described in the last century, is now often diagnosed. Medical treatment with beta-blockers, especially with propranolol, has been in use for more than 10 years. Long-term follow-up, however, has cast considerable doubt on the effectiveness of this therapy. It seems that the progression of the disease cannot be stopped and that a recurrence of symptoms is common (Edwards *et al.*, 1970; Goodwin, 1970; Hubner *et al.*, 1973; Stenson *et al.*, 1973; Morrow *et al.*, 1975; Loogen *et al.*, 1976; Rothlin *et al.*, 1976; Sowton, 1976).

Experimentally, it has been shown that certain forms of cardiomyopathy can be prevented with calcium inhibitor drugs. This was shown for the hereditary cardiomyopathy of the Syrian hamster (Lossnitzer, 1975). Recently, similar findings were reported in the cardiomyopathy induced by doxorubicin (Daniels *et al.*, 1976). Though there are differences between experimentally induced cardiomyopathy and that found in humans, the myocardial damage may be the consequence of a similar mechanism in which the calcium ion plays an important role (Fleckenstein, 1969; Witzke and Kaye, 1976; Wrogemann and Pena, 1976).

Patients with HOCM may have a remarkably high left ventricular contractility even in the advanced stages of the disease. Their sensitivity to catecholamines and to digitalis is also well known. These features of the disease may be related to an increased availability of intracellular calcium. After a pilot study, a clinical trial with the calcium inhibitor, verapamil, was initiated (Kaltenbach *et al.*, 1976).

Methods

Twenty-two patients, 18 men and 4 women, aged 19 to 44 years, were studied. Informed consent was obtained from all patients.

Symptoms were evaluated by means of a questionnaire. Electrocardiograms were recorded every 3 months with special attention to accurate calibration. In addition, phonocardiograms, carotid pulse tracings, and M mode echocardiograms (Picker System) were recorded.

Heart volume, calculated from chest *x*-rays films in the supine position at a tube-film distance of 2 m (Klepzig and Frisch, 1965), was determined every 6 months. In addition, conventional chest *x*-ray films in the standing position were taken. Before treatment with verapamil, right and left heart catheterisation was done in all patients, and selective coronary arteriograms (Sones technique) and biplane cine left ventriculograms were obtained. Right ventriculograms were taken only when a systolic pressure gradient was recorded within the right ventricle.

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In 10 patients, right and left heart catheterisation was repeated after 14 to 24 months (average 19 months) treatment with verapamil. The follow-up study also included selective coronary arteriography and ventriculography. In addition, left ventricular contractility was studied at rest and during exercise by means of a Millar double-tip catheter. The patients were exercised for 6 minutes on a bicycle ergometer in the supine position at a workload of 50 to 100 watts. After recovery from the first exercise test, 10 mg verapamil was injected intravenously and a second exercise test was performed using the same workload and the same duration of exercise. Pressure and contractility (dP/dt max and $dP/dt/P$) were recorded through the Millar catheter, with one transducer in the apex and the other in the outflow tract of the left ventricle. Contractility reserve is defined as the difference between dP/dt max at rest and dP/dt max during exercise.

Coronary artery diameters were measured in different sites from the cineangiograms using a TV camera mounted on a cineprojector for high magnification. Left ventricular muscle mass was calculated from left ventricular free wall and left ventricular end-diastolic volume. Left ventricular end-diastolic volume and left ventricular end-systolic volume were determined from outlines of the left ventricle in two planes (RAO 40° and LAO 50°). For these calculations, Simpson's rule using the computer system 'Volumat' (Siemens) was applied. *X*-ray magnification factor was determined (Kaltenbach *et al.*, 1975) and used for calculation of coronary diameter, left ventricular volume, and left ventricular muscle mass (see Fig. 5).

Medication

Before the study, most patients had been treated for several months or years with beta-blocking agents, such as propranolol (120 to 240 mg per day) or pindolol (7·5 to 15 mg per day). In patients receiving a beta-blocker this treatment was stopped for at least one week before verapamil[1] was started. After one week of treatment with verapamil 80 mg t.d.s., the dose was increased to 160 mg t.d.s. (480 mg per day). In some patients, the dose was further increased after several months to 720 mg per day. The drug was always administered orally.

Statistical methods

Student's t test was used to analyse the differences in the mean values before and after treatment. The criterion of significance was $P < 0.05$. Every patient served as his own control.

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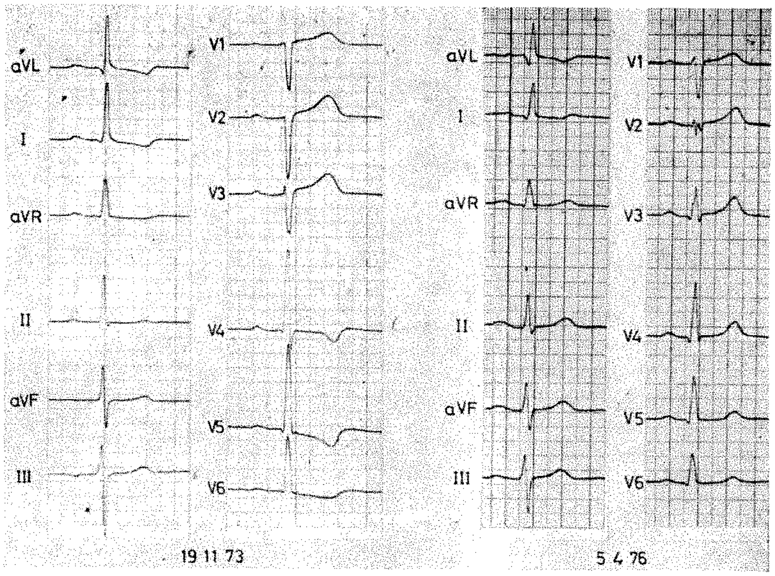
[1] Knoll AG, Pharmaceuticals, D-6700 Ludwigshafen, West Germany.



19 11 73

5 4 76

Fig. 1 *Electrocardiogram from a male patient aged 45 with hypertrophic obstructive cardiomyopathy before and after treatment with verapamil.*

Results

SYMPTOMS

Sixteen patients were symptomatic. Eleven of these patients reported lessening or complete relief of chest pain or breathlessness on effort. Six patients had only minor subjective symptoms and noticed no essential change during treatment.

HEART RATE AND BLOOD PRESSURE

The average heart rate decreased from 68 to 65 beats/min. Statistically, this difference was not significant. Blood pressure fell to normal in one patient with moderate hypertension during treatment with verapamil. No change was observed in the remaining patients.

ELECTROCARDIOGRAM

After an average period of treatment of 15 months (4 to 24 months) a significant reduction in QRS amplitude was observed. The average Sokolow index (sum of maximal S and R deflections in leads V1 to V6) decreased from 4·2 to 3·8 mV. Twelve patients showed a decrease in QRS amplitude, in 5 patients this was unchanged, and 3 patients showed an increase in amplitude. The reduction of QRS amplitude was accompanied by a tendency for ST segments to return towards normal; Fig. 1 shows a typical example. The changes in QRS amplitude during treatment with verapamil were compared with the values during previous treatment with beta-blockers (Fig. 2). During treatment with beta-blockers most patients had shown an unchanged or even increased QRS amplitude. In contrast, a distinct decrease was observed during verapamil treatment.

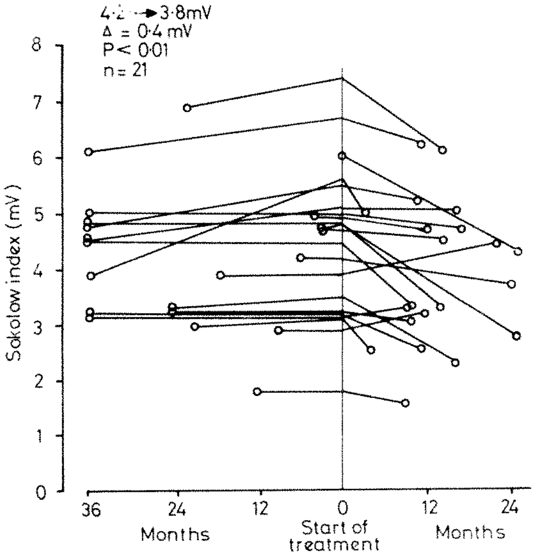


Fig. 2 *Sokolow index in the praecordial electrocardiogram before and during verapamil treatment.*

PHONOCARDIOGRAM, CAROTID PULSE, AND ECHOCARDIOGRAM

The systolic murmur of HOCM did not disappear during treatment with verapamil, but in some patients there was a decrease in intensity of the murmur. Carotid pulse tracings showed no significant change. No conclusions can be drawn from a limited number of echocardiographic studies.

CHEST *x*-RAY AND HEART VOLUME

Heart volume was calculated in 21 patients from chest *x*-ray films in the supine position. Measurements made before and after an average of 14 months treatment (2 to 24 months) are shown in Fig. 3. On average, heart volume decreased from 858 to 766 ml per 1·73 m^2; in 16 patients there was a decrease, in 3 patients an increase, and in 2 no change in heart volume. Conventional chest *x*-ray films in the standing position showed no essential change, and there were no signs of pulmonary congestion.

HEART CATHETERISATION

Catheterisation data obtained in 10 patients at the second study were compared with those obtained at the first catheterisation (Table). In 4 patients, this had been performed more than one year before the beginning of treatment with verapamil.

In 5 patients the systolic pressure gradient in the left ventricle was smaller, in 2 it was unchanged, and in 1 it was greater. In 1 of the 10 patients, no gradient was present, and in 1 the

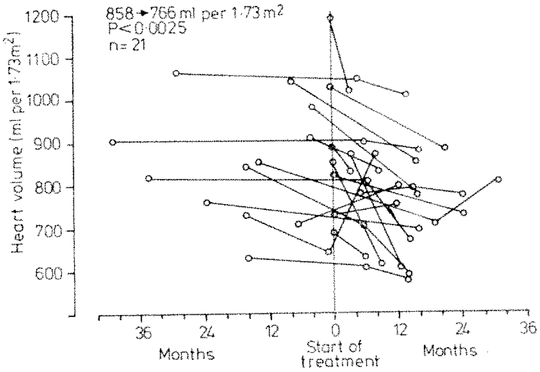


Fig. 3 *Heart volume before and during verapamil treatment.*

Table *Haemodynamic and other measurements before and after verapamil treatment*

Case no.	*Beginning of verapamil treatment*	*Duration of treatment (mth)*	*Dates of catheterisation*	*LVEDV (ml per 1·73 m²)*	*EF (%)*	*LV muscle mass (ml per 1·73 m²)*
1	6.1975	14	b 10.11.1972	105	63	148
			a 31.8.1976	142	63	101
2	4.1975	15	b 7.3.1974	85	78	122
			a 14.9.1976	89	76	110
3	9.1974	24	b 11.12.1974	72	75	151
			a 7.9.1976	95	85	104
4	9.1974	24	b 19.8.1974	149	88	154
			a 7.9.1976	146	93	112
5	3.1974	23	b 25.6.1973	86	89	126
			a 27.9.1976	90	88	138
6	7.1975	16	b 26.3.1975	201	80	417
			a 21.9.1976	109	71	318
7	4.1975	19	b 9.3.1972	109	85	349
			a 23.11.1976	131	86	296
8	6.1975	17	b 29.5.1972	80	89	91
			a 9.11.1976	120	90	134
9	5.1975	18	b 29.7.1971	117	90	232
			a 9.11.1976	179	91	301
10	6.1975	15	b 11.12.1974	98	90	250
			a 14.9.1976	114	90	213
Average			b	110	82	204
			a	121	83	182

measurement could not be repeated. As shown in Fig. 4, the gradient at rest and after provocation did not always change in the same manner.

Left ventricular muscle mass decreased in 7 patients and increased in 3 (Fig. 5). In the 3 patients with increased left ventricular muscle mass the first catheterisation had been performed 2 to 3 years before the beginning of verapamil treatment. A further increase of left ventricular muscle mass may have occurred before treatment with verapamil. Because of a pronounced reduction in wall thickness, muscle mass even decreased in some patients with increased left ventricular end-diastolic volume. Left ventricular end-diastolic pressure and ejection fraction were not affected by the treatment.

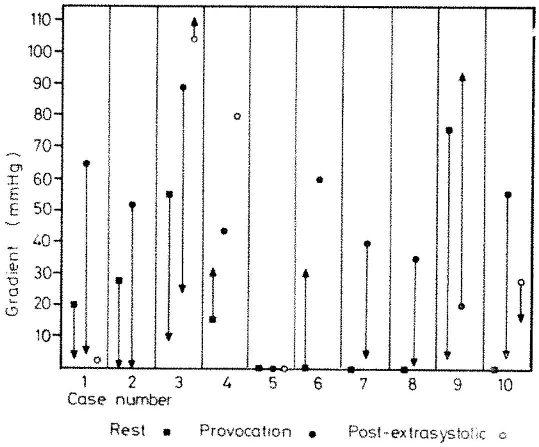


Fig. 4 *Systolic pressure gradients within the left ventricle as measured at the times of the first and second catheterisation. Before verapamil,* ■ = *rest,* ● = *provocation,* ○ = *post-extrasystolic. After verapamil, gradients shown by arrow* (↑ *or* ↓).

SELECTIVE CORONARY ARTERIOGRAPHY

Two independent investigators measured the coronary artery diameters at 5 different sites (Fig. 7). The investigators were not aware whether they were analysing the first or the second coronary arteriogram of a given patient. Correction was made for differences in x-ray magnification. Premedication was identical in all patients. Seven patients showed a decrease, 1 an increase, and 2 no change in coronary artery diameters (Fig. 7). On the average, both right and left coronary arteries were significantly reduced in diameter (8 and 9% respectively) and in cross-sectional area (15 and 17%). A typical example is shown in Fig. 8.

The results are summarised in the Table. In general there are parallel reductions in interventricular gradient, left ventricular muscle mass, QRS amplitude, heart volume, and coronary artery diameter, during oral verapamil treatment.

EFFECT OF INTRAVENOUS VERAPAMIL ON LEFT VENTRICULAR CONTRACTILITY

As verapamil can be shown to reduce contractility, 11 patients with HOCM were studied using a Millar double-tip catheter. Eight of these patients had been treated with oral verapamil before this investigation; 3 had not been treated. Haemodynamic measurements were made at rest and on exercise. After recovery, 10 mg verapamil were given intra-

	Coronary artery diameter		Gradient (mmHg)				Sokolow index		Heart volume	
hange)	(mm)	(% change)	Rest		Provocation		(mV)	(% change)	(ml)	(% change)
	5·9	−17	20	↓	65	↓	5·3	−11	817	−18
	4·9		4		6		4·7		669	
	4·9	−14	28	↓	52	↓	3·5	−34	763	− 9
	4·2		0		0		2·3		694	
	3·8	− 5	56	↓	89	↓	6·0	−33	820	−11
	3·6		9		24		4·0		731	
	3·9	0	15	↑	43	=	4·2	0	711	− 8
	3·9		32		43		4·2		657	
	4·2	−26	0	=	0	=	2·9	+ 7	853	− 5
	3·1		0		0		3·1		810	
	6·0	− 3	0	↑	60	=	> 5	−	1045	−18
	5·8		32		60		5		856	
	3·4	0	0	=	40	↓	3·2	−22	645	+26
	3·4		0		4		2·5		872	
	5·0	−10	0	=	35	↓	5·5	− 5	901	− 2
	4·5		0		1		5·2		880	
	2·9	+15	75	↓	20	↑	3·6	+27		
	3·4		4		93		4·9		960	
	4·1	−12	0	=	56	↓	1·7	+24	633	− 8
	3·6		0		4		2·1		581	

venously and a second exercise test was performed 10 minutes later. Left ventricular systolic and end-diastolic pressures fell from 147 to 132, and 20 to 16 mmHg, respectively. The intraventricular pressure gradient remained unchanged. The heart rate on exercise was significantly higher after verapamil. Contractility was unchanged after verapamil and this was so at rest as well as during exercise.

In contrast, beta-blocking drugs cause a distinct reduction in contractility at rest and a complete abolition of contractility reserve, as measured by identical methods.

SIDE EFFECTS

One patient had a first degree atrioventricular block with a PR interval of 0·3 s during administration of verapamil in a dose of 480 mg per day. After reduction of the daily dose to 240 mg, the PR interval became normal. In the remaining patients there was no change in PR interval. Five patients complained of dizziness, nausea, headache, or chest pain during the first weeks of treatment. These symptoms disappeared while treatment continued.

Discussion

It is our clinical impression from this study that verapamil offers a better therapeutic approach to HOCM than the treatment with beta-blockers. Since most of the patients had been on conventional beta-blocker therapy before starting treatment with verapamil, the improvement in subjective and objective indices on verapamil could be compared with results of this preceding treatment. Because patients and investigators regarded beta-blockers as effective treatment, a placebo effect of verapamil seems unlikely. Subjective symptoms disappeared or lessened considerably in two-thirds of the patients who had been symptomatic on beta-blocker treatment. Usually, it took several weeks of treatment with verapamil before subjective improvement was noticed. The disappearance or lessening of left ventricular hypertrophy on the electrocardiogram was very impressive in some patients. In others, only slight changes were noted; this was particularly true for patients whose electrocardiograms did not show a typical left ventricular hypertrophy pattern. The improvement in the electrocardiogram was remarkable when compared with the finding of unchanged or increasing QRS amplitudes during treatment with beta-blockers.

Using chest x-ray films in the supine position, a significant decrease in heart size was noted, whereas conventional chest x-ray films showed no change in size or configuration of the heart. Radiographic signs of left ventricular failure were not observed during verapamil treatment. Since acute drug administration can influence heart size, all heart volume determinations were made 2 days after withdrawal of verapamil. The same procedure was adopted for heart volume determination during the preceding period of beta-blocker therapy. The diminished heart volume must therefore be attributed to a sustained reduction in heart size and not to an acute effect of verapamil. Since beta-blockade increases heart size, one could argue that the reduction in heart size might be attributed to a withdrawal of beta-blockers. However, the beta-blocker

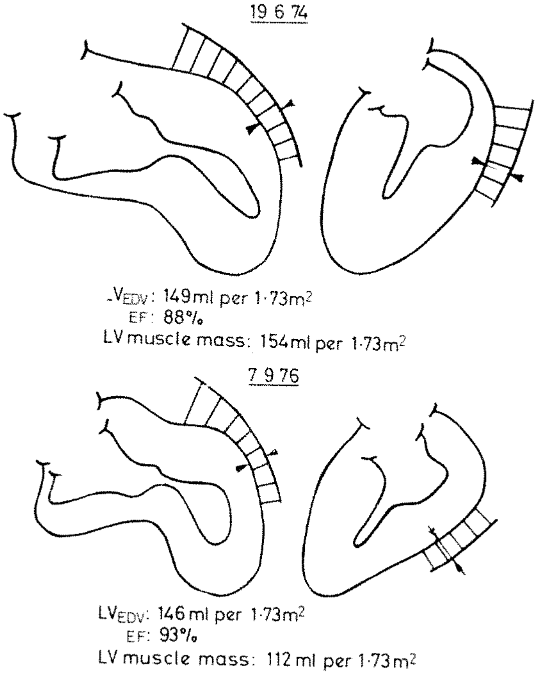


Fig. 5 *End-diastolic and end-systolic contours (RAO and LAO views) of the left ventricle in a patient (case 4) before and after treatment. The wall thickness is shown outside the end-diastolic contour. Left ventricular muscle mass was calculated from end-diastolic volume and left ventricular wall thickness in the RAO (anterior wall) and LAO (posterior wall). After treatment, a decrease in left ventricular muscle mass is observed while there is little change in end-diastolic volume. Volume calculations were made applying Simpson's rule by means of a computer system. The* x-ray *magnification was determined by observing the movement of the catheter tip located in the left ventricle when the* x-ray *table was moved a distance of 7 cm (19.6.74) or 6 cm (7.9.76).*

was discontinued before the heart volume determination and the reduction in heart size occurred also in patients who were not on a beta-blocker before treatment with verapamil.

The left ventricular pressure gradients recorded at left heart catheterisation before and after verapamil treatment did not show the same consistent improvement as did the subjective symptoms, electrocardiogram, and heart volume, but pressure gradients often do not reflect the severity of the disorder. However, in several patients the first catheterisation had been done 1 to 3 years before verapamil treatment, and further deterioration may have occurred during this time.

When coronary artery diameters are measured all factors which can influence the dimensions of coronary arteries have to be taken into consideration. Vasodilators, such as glyceryl trinitrate, increase coronary diameter (Gensini, 1975). A quantitative assessment of coronary artery dimensions is, therefore, only possible when the influence of any acutely administered drug can be ruled out. In addition, variations in *x*-ray magnification have to be taken into account. There was a genuine reduction in coronary artery cross-sectional area of about 16 per cent during treatment with verapamil, when measurements were made carefully observing all the above-mentioned precautions. In an earlier study (Kober *et al.*, 1973), a direct relation between left ventricular muscle mass and coronary artery cross-sectional area was shown (Fig. 6). It could, therefore, be assumed that the observed reduction in coronary artery dimension was the consequence of a decrease in ventricular muscle mass. This decrease in left ventricular muscle mass was confirmed by measurements computed from the left ventricular angiograms. The observation of a reduction of coronary artery diameter provides evidence of a reduction in left ventricular hypertrophy by a method which is completely independent of all other measurements such as QRS voltage, heart volume, or left ventricular muscle mass determined angiocardiographically.

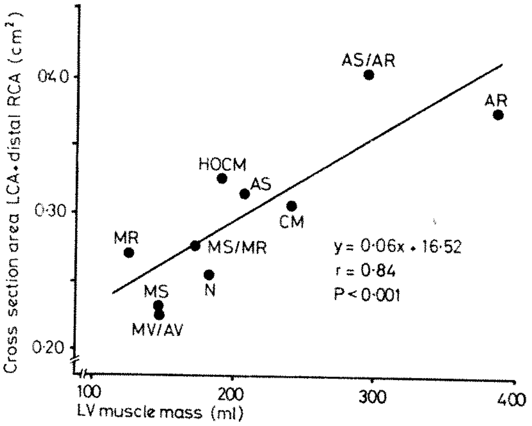


Fig. 6 *Relation of coronary artery cross-section area and left ventricular muscle mass in different groups of patients (Kober* et al., *1973). MS, mitral stenosis; MR, mitral regurgitation; MV, mitral valve disease; AS, aortic stenosis; AR, aortic regurgitation; AV, aortic valve disease; CM, cardiomyopathy; N, normal.*

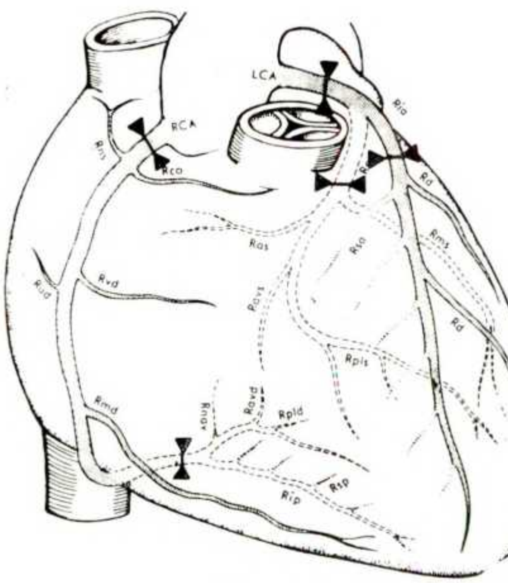
Whenever new drugs are administered, a drug-free interval is desirable to assess the efficacy of the new medication. In the present investigation, however, we chose not to interrupt the treatment; the subjective and objective changes following the change of treatment have to be interpreted in the light of the changes resulting from previous treatment with beta-blockers and its subsequent discontinuance. It might be argued that the dose of 240 mg propranolol per day was not as high as some authors would have preferred. This dose, however, was not exceeded because testing of antianginal activity of beta-blockers by our own group had clearly shown that larger doses are only slightly more effective (Kaltenbach, 1977).

It is concluded from analysis of patients' symptoms, clinical data, and a variety of objective measurements that the treatment of HOCM with verapamil is effective and seems better than beta-blocker treatment.

In order to investigate the mechanism of action of the drug, we observed the acute effects of intravenous verapamil on left ventricular contractility and aortic and left ventricular pressures. There was no significant change in contractility, but left ventricular systolic pressure decreased slightly (10%) and left ventricular end-diastolic pressure conspicuously (20%).

This fall in left ventricular systolic and end-diastolic pressures points to a peripheral action of the drug, and is probably partly responsible for its beneficial action. On the other hand, however, it is also possible that the calcium inhibitor action with negative inotropic effect on the myocardium was obscured by a reflex sympathetic response induced by the fall in blood pressure.

It remains to be established which patients will respond best to verapamil, which patients may not respond, and which patients may require combined treatment with verapamil and beta-blockers. For this reason, we have initiated a multicentre co-operative study, in which one group of patients is



	Before		After		
			Diameter		
LCA	4·40	→	4·03 mm²	-9%	P<0·01
RCA	2·72	→	2·50 mm²	-8%	P<0·01
			Cross-section area		
LCA	15·19	→	12·58 mm²	-17%	P<0·01
RCA	5·81	→	4·91 mm²	-15%	P<0 01

Fig. 7 *Measurement of coronary artery diameter in 5 different locations. The reduction in diameter and cross-section area after verapamil treatment is calculated from mean values for the right (RCA) and left (LCA) coronary artery in 10 patients.*

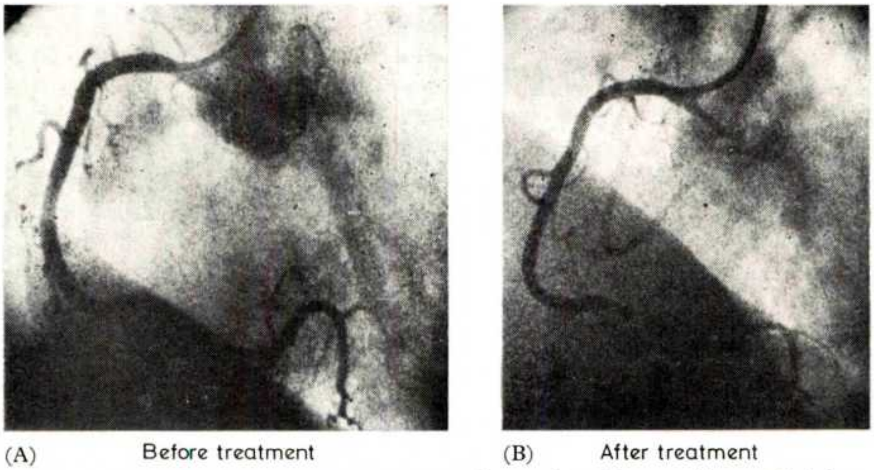

(A) Before treatment (B) After treatment

Fig. 8 *Example of reduction in coronary artery diameter in a 48-year-old man (A) before treatment, (B) after treatment.*

treated with verapamil and another matched group with beta-blockers, and which will probably give further information within the next two years.

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Addendum

Since the submission of this paper for publication, the number of patients treated with verapamil has increased from 22 to 39, and duration of follow-up now ranges from 1 to 100 months (mean 26·4 months). Experience with additional patients and longer follow-up confirms the reported favourable results. In 4 patients, treatment was discontinued because of non-cardiac illnesses: in these patients deterioration ensued. Recently serum verapamil levels have been measured (B. G. Woodcock); there appears to be a correlation between verapamil level and clinical improvement.

British Heart Journal, 1979, **42,** 43-50

Haemodynamic effects of dobutamine with special reference to myocardial blood flow

A comparison with dopamine and isoprenaline

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SUMMARY The haemodynamic effects of dobutamine (2·5 to 10 μg/min per kg) were determined in 5 patients without cardiac failure who were undergoing cardiac catheterisation for suspected coronary disease. Myocardial blood flow was determined by the coronary sinus thermodilution technique. Data were compared with those from two groups of 5 patients who received dopamine (4-8 μg/min per kg) and isoprenaline (0·005-0·025 μg/min per kg). Each drug was given in a lower and a higher dose, and all increased mean cardiac index (dobutamine, 18% and 39%; dopamine, 11% and 23%; isoprenaline, 15% and 44%). These increases were associated with significant increases in mean myocardial oxygen consumption (dobutamine, 38% and 61%; dopamine, 25% and 62%; isoprenaline, 20% and 45%). Mean myocardial blood flow was increased by each drug but mean myocardial oxygen extraction was decreased by isoprenaline, was increased by dopamine, and was unchanged by dobutamine. Each inotropic agent has a similar effect on myocardial oxygen consumption, but isoprenaline has a direct coronary vasodilator action while dopamine has a coronary vasoconstrictor action. Dobutamine has no direct effect upon coronary vascular tone.

Dobutamine is a new inotropic agent which has been shown to be effective in improving left ventricular function in patients with congestive heart failure (Akhtar *et al.*, 1975; Beregovich *et al.*, 1975; Leier *et al.*, 1977). Dopamine, another inotropic sympathomimetic amine, also improves left ventricular function in patients with congestive heart failure (Loeb *et al.*, 1971; Holzer *et al.*, 1973; Beregovich *et al.*, 1974).

In the selection of an inotropic drug for use in patients with acute myocardial infarction an important consideration is its possible effect on infarct size. Inotropic drugs have a potential for increasing myocardial oxygen consumption (Braunwald, 1971), thereby increasing oxygen demand in excess of supply with a consequent increase in infarct size (Maroko *et al.*, 1971; Maroko and Braunwald, 1973). Such drugs may also increase myocardial ischaemic injury through a primary effect on the coronary circulation. For example, isoprenaline has been shown to increase myocardial ischaemia in dogs through a 'coronary steal' effect whereby blood is shunted away from ischaemic areas by dilatation of adjacent resistance arterioles in normal myocardium (Sharma *et al.*, 1971; McClenathan *et al.*, 1977). Conversely, a coronary vasoconstrictor effect may increase ischaemic injury by reducing coronary flow relative to myocardial oxygen demand.

This study was performed, therefore, to determine the haemodynamic effects of dobutamine with special reference to its effects on coronary dynamics, and to compare these effects with those of dopamine and isoprenaline.

Patients and methods

Fifteen patients without congestive heart failure, undergoing cardiac catheterisation for suspected coronary artery disease, were studied. Informed consent was obtained in all cases. All drugs were withdrawn 48 hours before the study, except for 15 mg diazepam given as premedication.

One group of 5 patients received isoprenaline, one group of 5 received dobutamine, and another received dopamine. Drug doses were selected according to the individual's response. An attempt was made to match increases in cardiac output for the 3 drugs.

Patient data are presented in Table 1 together with drug doses for individual patients.

Pressures were measured using Bell and Howell transducers set for zero at mid-chest level, and

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Table 1 *Patient data*

Case no.	*Age*	*Sex*	*Coronary angiogram*	*Drug dose µg/min per kg* *1*	*2*
Isoprenaline					
1	43	M	50% LAD, 75% Cx	0·006	0·012
2	58	M	50% LAD	0·007	0·014
3	41	M	Normal	0·025	0·05
4	37	M	Normal	0·005	0·01
5	50	M	75% Cx, 75% RCA	0·007	0·014
Dobutamine					
6	55	M	100% LAD, 100% RCA, 75% 1st and 2nd lateral Cx	5	10
7	33	M	75% LAD	5	10
8	39	M	50% lateral Cx, 75% RCA	5	10
9	51	F	Normal	5	10
10	36	M	Normal	2·5	5
Dopamine					
11	34	M	Normal	4	8
12	44	M	100% LAD, 100% RCA	4	8
13	48	M	Normal	4	12
14	56	M	90% LAD, 90% lateral Cx	4	8
15	46	M	90% LAD, 75% 1st lateral Cx	4	8

LAD, left anterior descending; Cx, circumflex; RCA, right coronary artery.

recorded on a Mingograf 82 recorder at paper speeds of 25 and 50 mm/s. Systemic arterial pressure was recorded using a Desilets Hoffman cannula placed in the femoral artery. Pulmonary arterial and pulmonary artery wedge pressures were recorded using a flow-directed thermodilution catheter advanced to the pulmonary artery from the femoral vein. Cardiac output was measured by the thermodilution technique (Ganz and Swan, 1972) using a Waters computer.

Myocardial blood flow was determined by the method described by Ganz *et al.* (1971). To make this determination a special catheter was positioned in the coronary sinus via a left antecubital vein. Coronary sinus flow was determined by a continuous thermodilution technique using the formula described below. Since the coronary sinus drains nearly all of the left ventricular myocardium (Hood, 1968), coronary sinus flow may be assumed to represent left ventricular myocardial blood flow. In order to include the contribution to coronary sinus flow of the posterior interventricular vein, the catheter was first positioned high in the great cardiac vein and was then slowly withdrawn toward the orifice of the coronary sinus. The point at which there was a sudden and distinct increase in flow (indicated by an increase in the temperature of the mixture of blood and injectate recorded by the downstream thermistor as it passed the junction of the posterior interventricular vein and coronary sinus) determined the position at which flow was measured. Experience in this laboratory has shown that coronary sinus flow accurately represents myocardial blood flow over a wide range of flows in patients with and without coronary artery disease (Stephens *et al.*, 1978).

The coronary sinus catheter was used to measure coronary sinus pressure.

Mean pressures were obtained by electronic integration. Blood oxygen content was measured by the fuel-cell technique (Lex O_2 Con).

Lead II of the electrocardiogram was recorded for heart rate measurement and for observation of possible ST-T changes.

PROCEDURE

After left ventriculography and coronary arteriography (Judkins' technique) 30 minutes were allowed for recovery from the haemodynamic effects of contrast media (Mullins *et al.*, 1972).

Control recordings of heart rate, pressures, and coronary sinus flow were made. Cardiac output determinations were made in triplicate. Simultaneous systemic arterial and coronary sinus blood samples were withdrawn for oxygen content measurement.

A lower dose followed by a higher dose of drug was infused for periods of 10 minutes, measurements being repeated during each period.

There were no complications from the study. No patient complained of angina and no ST-T changes were observed on the electrocardiogram during the periods of drug infusion.

CALCULATIONS

Systemic vascular resistance, coronary vascular resistance, and left ventricular stroke work index were calculated using standard formulae.

Myocardial oxygen consumption (ml/min) = product of myocardial blood flow (coronary sinus flow) and the coronary arteriovenous oxygen content difference (AVO_2 diff.).

Myocardial oxygen extraction (per cent) = AVO_2 diff./arterial oxygen content × 100.

$$\text{Coronary sinus flow (ml/min)} = \frac{T_M - T_I}{T_B - T_M} \times K \times Q_I$$

where T_M = temperature of the mixture of blood and injectate (°C);
T_I = temperature of injectate (°C);
T_B = temperature of blood (°C);
K = a constant (1·08);
Q_I = rate of infusion of the injectate (35 ml/min)

Statistical analysis was by the paired Student's t test and the Mann-Whitney U test.

Table 2 *Haemodynamic effects of isoprenaline*

	Control	*Lower dose*	*Higher dose*
Systemic haemodynamics			
Heart rate (beats/min)	72 ± 5·6	78 ± 5·6**	92 ± 8·3***
Systemic arterial mean pressure (mmHg)	93 ± 3·7	92 ± 3·5	91 ± 4·6
Pulmonary artery wedge mean pressure (mmHg)	12 ± 1·5	12 ± 1·5	11 ± 1·5
Cardiac index (1/min per m^2)	3·4 ± 0·4	3·9 ± 0·6	4·9 ± 0·08***
Stroke volume index (ml per m^2)	47 ± 5·3	50 ± 6·8	54 ± 7·1
Systemic vascular resistance (dynes s cm^{-5})	1181 ± 229	1033 ± 221***	831 ± 200***
Left ventricular stroke work index (gm per m^2)	42 ± 5·8	44 ± 7·2	49 ± 6·9
Coronary haemodynamics			
Coronary sinus flow (ml/min)	165 ± 12·6	219 ± 19·8**	277 ± 33·2***
Myocardial oxygen consumption (ml/min)	20 ± 1·6	24 ± 2·4**	29 ± 3·2***
Myocardial oxygen extraction (%)	66 ± 4·2	59 ± 4·2	56 ± 3·6
Coronary vascular resistance (dynes s cm^{-5}) ($\times 10^{-3}$)	45 ± 3·3	35 ± 4·3***	28 ± 3·8****
Coronary sinus mean pressure (mmHg)	5 ± 1·0	3 ± 0·9	5 ± 0·8

** $P < 0·02$; *** $P < 0·01$; **** $P < 0·001$.
All values are shown as mean ± SEM for 5 patients.

Results

CINEANGIOGRAPHIC DATA

Left ventriculography showed all patients to have a normal ejection fraction.

Coronary arteriographic findings are shown in Table 1.

SYSTEMIC HAEMODYNAMIC DATA

Isoprenaline (Table 2)

There were dose-related increases in mean heart rate (8% and 28%) and cardiac index (15% and 44%). Though mean stroke volume increased (6% and 15%) these changes were not significant. Mean values for pulmonary artery wedge mean pressure and systemic arterial mean pressure were unchanged. Mean systemic vascular resistance fell significantly (13% and 30%). Mean left ventricular stroke work index increased (6% and 17%) but these changes were not statistically significant.

Dobutamine (Table 3)

Mean heart rate increased slightly (3% and 17%) but these changes were not significant. There were dose-related increases in mean cardiac index (18% and 39%), though the further increase with the higher dose was not statistically significant. Changes in mean stroke volume index reflected this pattern (14% and 22%). Systemic arterial mean pressure increased significantly (mean 23% and 26%). There were no significant changes in mean values for pulmonary artery wedge mean pressure or systemic vascular resistance. Mean left ventricular stroke work index increased significantly (22% and 53%).

Dopamine (Table 4)

Dopamine produced no significant change in mean heart rate. Mean cardiac index increased (11% and 23%), but as with dobutamine the increase with the higher dose was not statistically significant. Mean stroke volume index increased significantly (10% and 18%). Mean values for systemic arterial mean

Table 3 *Haemodynamic effects of dobutamine*

	Control	*Lower dose*	*Higher dose*
Systemic haemodynamics			
Heart rate (beats/min)	71 ± 6·2	73 ± 8·2	80 ± 8·0
Systemic arterial mean pressure (mmHg)	83 ± 6·8	102 ± 5·3**	105 ± 7·0**
Pulmonary artery wedge mean pressure (mmHg)	9 ± 1·7	10 ± 1·3	10 ± 1·5
Cardiac index (1/min per m^2)	3·3 ± 0·2	3·9 ± 0·3***	4·6 ± 0·7
Stroke volume index (ml per m^2)	49 ± 6·7	56 ± 7·6*	60 ± 11·1
Systemic vascular resistance (dynes s cm^{-5})	1090 ± 117	1118 ± 161	1044 ± 168
Left ventricular stroke work index (gm per m^2)	51 ± 7·1	70 ± 10·0**	78 ± 17·0*
Coronary haemodynamics			
Coronary sinus flow (ml/min)	112 ± 13	144 ± 24	169 ± 19**
Myocardial oxygen consumption (ml/min)	13 ± 2·6	18 ± 4·0*	21 ± 3·2**
Myocardial oxygen extraction (%)	64 ± 4·1	64 ± 4·1	65 ± 2·9
Coronary vascular resistance (dynes s cm^{-5}) ($\times 10^{-3}$)	61 ± 6·0	60 ± 11·1	49 ± 3·8
Coronary sinus mean pressure (mmHg)	5 ± 0·9	5 ± 1·3	4 ± 1·1

* $P < 0·05$; ** $P < 0·02$; *** $P < 0·01$.
All values are shown as mean ± SEM for 5 patients.

Table 4 *Haemodynamic effects of dopamine*

	Control	*Lower dose*	*Higher dose*
Systemic haemodynamics			
Heart rate (beats/min)	73 ± 3·3	72 ± 2·5	73 ± 4·2
Systemic arterial mean pressure (mmHg)	105 ± 5·5	97 ± 2·0	101 ± 3·5
Pulmonary artery wedge mean pressure (mmHg)	9 ± 1·6	9 ± 1·1	8 ± 1·0
Cardiac index (1/min per m^2)	3·5 ± 0·3	3·9 ± 0·3**	4·3 ± 0·4
Stroke volume index (ml per m^2)	49 ± 3·7	54 ± 2·9*	58 ± 4·1*
Systemic vascular resistance (dynes s cm^{-5})	1279 ± 158	1048 ± 77*	993 ± 73
Left ventricular stroke work index (gm per m^2)	61 ± 3·2	64 ± 3·5	74 ± 6·5
Coronary haemodynamics			
Coronary sinus flow (ml/min)	139 ± 15·5	162 ± 20·3	186 ± 18·3*
Myocardial oxygen consumption (ml/min)	16 ± 2·7	20 ± 3·2*	26 ± 3·0****
Myocardial oxygen extraction (%)	60 ± 2·6	65 ± 3·6	70 ± 2·9***
Coronary vascular resistance (dynes s cm^{-5}) ($\times 10^{-3}$)	60 ± 4·7	49 ± 6·0	42 ± 3·8***
Coronary sinus mean pressure (mmHg)	5 ± 0·6	5 ± 0·8	6 ± 1·1

* $P < 0·05$; ** $P < 0·02$; *** $P < 0·01$; **** $P < 0·001$.
All values are shown as mean ± SEM for 5 patients.

pressure and pulmonary artery wedge mean pressure were unchanged. Mean systemic vascular resistance fell (18% and 22%). Mean left ventricular stroke work index increased (5% and 21%) but these changes were not statistically significant.

CORONARY HAEMODYNAMIC DATA

Isoprenaline (Table 2)
There was a dose-related increase in coronary sinus flow in all patients (Fig. 2), mean values increased (33% and 68%). Myocardial oxygen extraction fell conspicuously in 3 patients, fell slightly with the higher dose in 1, and remained unchanged in 1 (Fig. 3); the fall in mean values (11% and 15%) did not quite reach statistical significance. There was a significant dose-related increase in mean myocardial oxygen consumption (20% and 45%). Mean coronary vascular resistance fell significantly (22% and 38%). Mean coronary sinus pressure was unchanged.

Dobutamine (Table 3)
Coronary sinus flow increased in 4 patients and fell slightly in 1 for the lower dose. The higher dose produced further increases in 3 patients (Fig. 2); mean values increased by 29 and 51 per cent. Myocardial oxygen extraction did not change significantly (Fig. 3). There were significant dose-related increases in mean myocardial oxygen consumption (38% and 61%). Mean coronary vascular resistance fell (2% and 20%) but the changes did not achieve statistical significance. Coronary sinus mean pressure was unchanged.

Dopamine (Table 4)
The pattern of changes in coronary sinus flow was similar to that found for dobutamine (Fig. 2); the mean increases were 16 and 34 per cent. Mean myocardial oxygen extraction increased significantly by 8 and 17 per cent (Fig. 3). Mean myocardial oxygen consumption increased significantly (25% and 62%). There were significant falls in mean coronary vascular resistance (18% and 30%). Coronary sinus mean pressure was unchanged.

Changes in mean values for cardiac index and myocardial oxygen consumption for the 3 drugs are

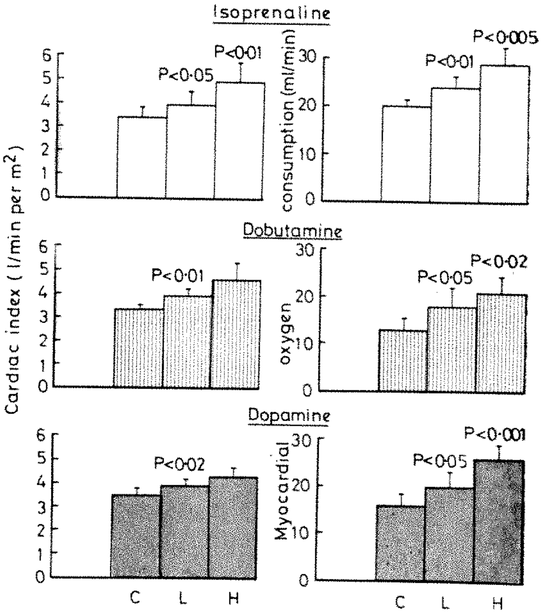

Fig. 1 *Changes in mean values for cardiac index for isoprenaline, dobutamine, and dopamine (5 patients in each group) compared with changes in myocardial oxygen consumption. C, control; L, lower dose; H, higher dose. Bars indicate mean ± SEM.*

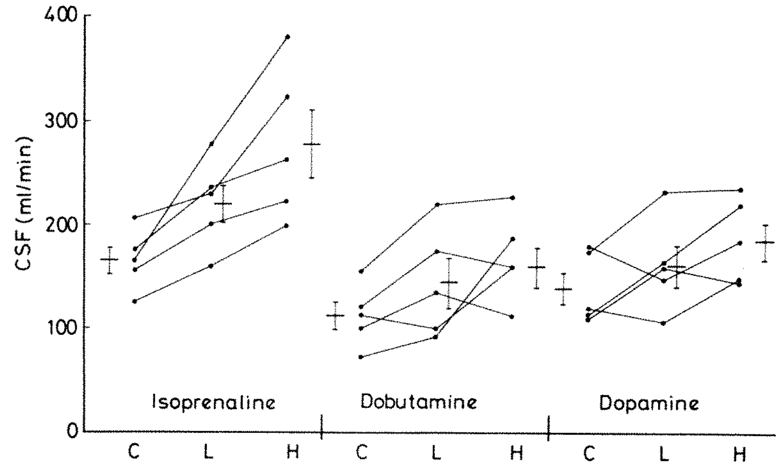

Fig. 2 *Changes in coronary sinus flow (CSF) in individual patients in isoprenaline, dobutamine, and dopamine groups. C, control; L, lower dose; H, higher dose. Bars indicate mean ±SEM.*

compared in Fig. 1. Changes in coronary sinus flow in individual patients for each drug are compared in Fig. 2 and in myocardial oxygen extraction in Fig. 3.

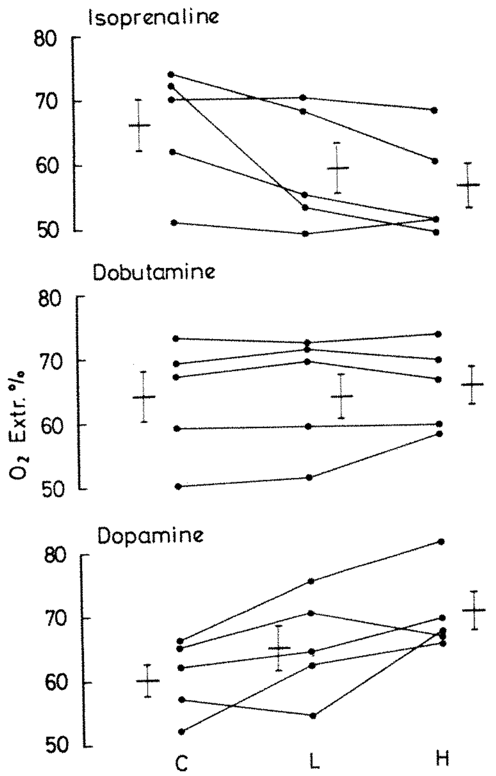

Fig. 3 *Changes in myocardial oxygen extraction (O_2 Extr.) in individual patients in isoprenaline, dobutamine, and dopamine groups. C, control; L, lower dose; H, higher dose. Bars indicate mean ±SEM.*

Statistical analysis showed no significant difference between the changes in myocardial oxygen consumption and coronary sinus flow for the three groups. However, the decrease in myocardial oxygen extraction with isoprenaline was significant compared with the other two groups, myocardial oxygen extraction being unchanged with dobutamine, and increased with dopamine.

Discussion

The increase in cardiac output produced by isoprenaline was achieved primarily by an increase in heart rate rather than stroke volume. In contrast, dobutamine and dopamine increased cardiac output principally by increasing stroke volume, there being little change in heart rate. The higher dose of dobutamine and dopamine did not in all cases increase cardiac output further; this may be related to a plateau in the inotropic effect, in the absence of an increase in heart rate or, as in some patients, with a slight decrease in heart rate possibly the result of a reflex vagal effect. Isoprenaline and dopamine produced significant falls in systemic vascular resistance, mean systemic arterial pressure being unchanged. Dobutamine, however, caused an increase in systemic arterial mean pressure with no change in systemic vascular resistance. This was an unexpected finding since dobutamine has been found to have little alpha-adrenergic effect on the peripheral vasculature (Tuttle and Mills, 1975). Previous studies in patients with congestive heart failure have shown systemic arterial pressure to be unchanged by dobutamine, though Loeb *et al.* (1975) found a significant increase in blood pressure in patients with normal left ventricular function, despite a fall in total systemic resistance. It thus appears that dobutamine may have a pressor action, though the reason for its manifestation in patients without but not in those with heart failure is not clear. It is probable that the fall in systemic vascular resistance observed with isoprenaline resulted from its beta$_2$-adrenergic effects, while that associated with dopamine was secondary to its specific (dopaminergic) action on certain vascular beds and to its weak beta$_2$-adrenergic action on others (Goldberg, 1972).

In this study the 3 sympathomimetic amines produced similar substantial dose-related increases in myocardial oxygen consumption. Since all 3 drugs have inotropic properties (Tuttle and Mills, 1975), augmented myocardial contractility was a common factor in producing such increases (Braunwald, 1971). Since heart rate is an important determinant of myocardial oxygen consumption (Sarnoff *et al.*, 1958), the increase in heart rate must have been an important additional reason for the observed increase in myocardial oxygen consumption produced by isoprenaline. However, this increase may have been counteracted by the peripheral vasodilator effect of isoprenaline, limiting the increase in systemic arterial pressure (Braunwald, 1971). The pressor effect of dobutamine and the slight increase in heart rate may have contributed to the increased myocardial oxygen consumption by increasing left ventricular afterload. The comparable increases in myocardial oxygen consumption produced by dopamine are more difficult to explain. Since indices of myocardial contractility were not measured in this study, a comparison of the contribution of the increases incontractility produced by the 3 inotropic agents to increases in myocardial oxygen consumption is not possible. However, it is conceivable that dopamine in the doses used produced greater augmentation in myocardial contractility than dobutamine or isoprenaline, accounting for its comparable effects on myocardial oxygen consumption.

Although the 3 drugs produced similar increases in myocardial oxygen consumption there were differences in their effects on the global myocardial oxygen demand/supply relation. Increased myocardial oxygen demand is met principally by an increase in myocardial blood flow, probably through autoregulation (Berne, 1964), myocardial oxygen extraction remaining constant (Katz and Feinberg, 1958; Stephens *et al.*, 1978). Changes in myocardial oxygen extraction produced by a drug may therefore be taken as evidence that the drug has a direct effect on the smooth muscle of the coronary vessels, distinct from its indirect effect on flow induced by changes in myocardial metabolic requirements (Gregg and Sabiston, 1956).

In the present study, dopamine increased coronary sinus flow and decreased coronary vascular resistance, associated with a significant increase in myocardial oxygen extraction. These observations suggest that while coronary vasodilatation occurred in response to augmented myocardial oxygen demand induced by dopamine, this response was attenuated by a direct coronary vasoconstrictor effect of the drug (Berne, 1958). Dopamine therefore adversely affected the balance between oxygen demand and supply for the myocardium as a whole. Isoprenaline also increased coronary sinus flow. However, compared with dopamine, there was an opposite effect upon myocardial oxygen extraction, suggesting that isoprenaline increased myocardial blood flow in excess of that required to meet increased myocardial oxygen demand and that the drug therefore has a direct coronary vasodilator action. Because dobutamine had no significant effect upon myocardial oxygen extraction, it may be concluded that the observed increases in coronary sinus flow were the result of augmented myocardial oxygen demand alone, and that dobutamine has no significant direct effect upon the coronary vasculature.

A coronary vasoconstrictor effect of dopamine has not previously been described, though a recent report (Wilkes *et al.*, 1976) described a reduction in coronary sinus oxyhaemoglobin saturation in dogs after dopamine infusion, despite an increase in myocardial blood flow. These authors, however, ascribed this finding to inadequate metabolic autoregulation. Brooks *et al.* (1969) found that dopamine increased myocardial blood flow in the dog commensurate with increases in myocardial oxygen consumption. Crexells *et al.* (1973) studied the haemodynamic and cardiac metabolic effects of dopamine in 10 patients with coronary disease. Though myocardial blood flow was not measured, these authors inferred that dopamine did not increase myocardial oxygen consumption as they found no significant change in the tension-time index. Furthermore, since there was no significant shift of myocardial lactate extraction to production, it was concluded that dopamine had no potential for increasing myocardial hypoxia. It is of interest to note, however, that in 9 of their 10 patients coronary sinus Po_2 fell slightly, while in 2 myocardial lactate extraction shifted to production.

The conclusion from the present study that dopamine has a coronary vasoconstrictor effect is supported by certain theoretical considerations. The coronary arterial vasculature of the dog has been shown to possess alpha and beta-adrenergic receptors (Gaal *et al.*, 1966). Since dopamine acts by releasing noradrenaline from myocardial storage sites (Tuttle and Mills, 1975), it has the potential to act indirectly on the coronary alpha-adrenergic receptors through the release of noradrenaline, thereby causing coronary vasoconstriction. This suggestion is substantiated by the reported coronary vasoconstrictor effect of noradrenaline in the dog (Berne, 1958) and in man (Yurchak *et al.*, 1964). In contrast, isoprenaline, because of its powerful beta-adrenergic effects, would be expected to dilate coronary arterial vessels. This effect has been reported in previous studies (Lewis *et al.*, 1961; Greenfield *et al.*, 1972). Tuttle and Mills (1975) showed that dobutamine, unlike dopamine, exerts its inotropic effect directly on the myocardium and not by the release of endogenous catecholamines. Vatner *et al.* (1974) reported that dobutamine increased coronary blood flow in the dog and that further increases could be elicited by unmasking a beta$_2$-adrenergic effect with practolol and phentolamine. Conversely, non-selective beta-adrenergic blockade with propranolol disclosed an alpha-adrenergic coronary vasoconstrictor effect. Thus dobutamine, like other sympathomimetic amines, may increase myocardial blood flow by increasing myocardial oxygen demand (autoregulation) or by a direct beta-adrenergic coronary vasodilator action. It also has, by virtue of its alpha-adrenergic properties, a potential for producing coronary vasoconstriction. The present study suggests that the coronary alpha- and beta-adrenergic effects of dobutamine are unimportant determinants of its effects on myocardial blood flow in man.

A major assumption in the interpretation of the results of the present study is that the presence and degree of coronary artery stenoses did not influence the observed changes in coronary sinus flow. Reports from this (Stephens *et al.*, 1978) and other laboratories (Yoshida *et al.*, 1971) have shown that large increases in coronary sinus flow can occur despite the presence of coronary artery disease. Furthermore, incremental increases in coronary sinus flow occur during successive increases of heart rate by atrial pacing up to the development of angina in patients with coronary disease. Such changes are identical to those found in patients with normal coronary arteries (Yoshida *et al.*, 1971). Since none of the patients in the present study developed angina during drug administration, it is unlikely that observed changes in coronary sinus flow were significantly modified by mechanical obstruction to flow by coronary disease. Further, the incidence and degree of coronary disease was roughly similar for the 3 patient groups, providing further evidence that differences in changes in coronary sinus flow relative to changes in myocardial oxygen extraction for the 3 drugs could be ascribed solely to differences in drug-induced changes in coronary arterial tone.

The results of this study may have clinical relevance with regard to patients with acute myocardial infarction. If dopamine causes coronary vasoconstriction when used in such patients, it may exacerbate the imbalance between oxygen demand and supply in ischaemic zones of the myocardium, thereby increasing infarct size. On the other hand, isoprenaline may exert its deleterious effect in patients with acute myocardial infarction (Mueller *et al.*, 1972) in part through a coronary vasodilator effect, thereby causing 'coronary steal'.

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Relation of isovolumic relaxation to left ventricular wall movement in man

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SUMMARY In order to determine the duration of isovolumic relaxation and its relation to left ventricular wall movement, 14 normal subjects, 44 patients with coronary artery disease, 16 with hypertension, and 10 with pure mitral stenosis were studied. Simultaneous echocardiograms, phonocardiograms, and apex cardiograms were performed, and the resulting traces digitised. In normal subjects, aortic valve closure (A_2) occurred at a mean of 40 ± 10 ms before the minimum left ventricular dimension, and the duration of isovolumic relaxation, taken as the period from A_2 to the onset of mitral valve cusp separation was a mean of 65 ± 15 ms. In patients with hypertension, the timing of aortic valve closure was normal, but isovolumic relaxation was prolonged to a mean of 105 ± 25 ms, so that mitral valve opening was significantly delayed, occurring at a mean of 80 ± 25 ms after the minimum left ventricular dimension. In patients with coronary artery disease, aortic valve closure was significantly delayed by a mean of 5 ± 40 ms with respect to the minimum left ventricular dimension. The mean duration of isovolumic relaxation did not differ significantly from normal, though the scatter was wide, but mitral valve opening was also delayed by a mean of 80 ± 35 ms. In these patients, there was a strong association between delay in aortic valve closure and abnormal wall movement during isovolumic contraction. In patients with mitral stenosis, aortic valve closure was significantly delayed (mean 30 ± 35 ms), but isovolumic relaxation was short (mean 40 ± 20 ms). Thus though delayed mitral valve opening occurs both in hypertension and coronary artery disease, its cause differs: in the former the cause is prolonged relaxation, while in the latter it is primarily incoordinate systolic wall movement, resulting in prolongation of ejection and delayed aortic valve closure, with respect to normal regions.

There is increasing evidence that abnormalities of left ventricular relaxation and filling may be major determinants of cardiac function in patients with heart disease. Though measurement of isovolumic relaxation time ought to prove a simple means of quantifying such abnormalities in clinical practice, previous studies in this area have been few. The problem of defining the timing of mitral valve opening at the onset of ventricular filling has been a difficulty; several previous studies have used the 'O' point of the apex cardiogram (Benchimol and Ellis, 1967), but more recently it has been shown that this may be open to considerable error (Friedman, 1970; Prewitt *et al.*, 1975). It was the purpose of the present study to reinvestigate this question, using echocardiography to time mitral valve opening, and thus determine the duration of isovolumic relaxation and its relation to left ventricular wall movement.

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Methods

Echocardiographic observations were made in 84 patients, comprising 4 groups: *Group 1:* 14 normal subjects. *Group 2:* 44 patients with coronary artery disease, confirmed by coronary arteriography. *Group 3:* 16 patients with severe hypertension, whose systemic arterial diastolic pressure had been greater than 120 mmHg before treatment. *Group 4:* 10 patients with pure mitral stenosis, confirmed at operation.

Echocardiograms were recorded with either a Cambridge Instruments or a Smith-Kline Ekoline 20 ultrasonoscope (frequency 2·25 MHz, repetition rate 1000/s). The output was displayed on a Cambridge Instruments strip-chart recorder operating at a paper speed of 100 mm/s with a simultaneous electrocardiogram. Records were taken with the patient in the 30 degree left oblique position. The transducer was directed so that the ultrasound beam passed through the left ventricular

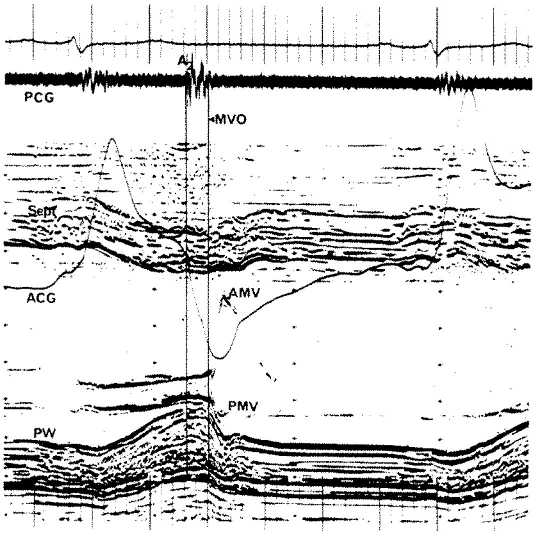

Fig. 1 *Echocardiogram of a normal subject showing septum (Sept), posterior left ventricular wall (PW), anterior mitral leaflet (AMV), and posterior mitral leaflet (PMV). Simultaneous phonocardiogram (PCG) and apex cardiogram (ACG) are also recorded. The duration of isovolumic relaxation is measured from the aortic component of second heart sound (A_2) to the time of initial separation of mitral valve leaflets (MVO).*

cavity at the level of the tips of the mitral leaflets. Mitral valve opening was taken as the time, to the nearest 5 ms, of separation of the anterior and posterior cusps at the onset of ventricular filling. Care was taken to produce clear, continuous endocardial echoes in order that they could be digitised (Fig. 1).

On all records, a simultaneous phonocardiogram was recorded, using a Cambridge microphone and a high frequency filter. The initial high frequency vibration of the aortic component of the record sound was taken as the onset of isovolumic relaxation (A_2). In normal subjects, and in 39 of the 44 patients with coronary artery disease, apex cardiograms were also recorded from the point of maximum impulse. A Cambridge Scientific Instruments transducer was used, with a time constant of 4 s and a lower frequency limit of 0·05 Hz.

DIGITISING METHODS

Echocardiograms and apex cardiograms were digitised as previously described (Gibson and Brown, 1973; Venco *et al.*, 1977). Plots were made of left ventricular dimension and its rate of change. The time relations between left ventricular dimension and the apex cardiogram were displayed in the form of a loop, which allowed changes in dimension during isovolumic contraction and early relaxation to be readily appreciated. From the plots, the following information was derived.

(1) The isovolumic relaxation time, taken as the interval between A_2 and the onset of mitral valve opening. The timing of these two events was noted on all echocardiograms, and appeared on the final digitised plots as two crosses. The effect of spontaneous alteration of the RR interval was further investigated by recording simultaneous phonocardiograms and mitral echograms using the methods described above, in 42 additional normal subjects.

(2) The time interval from minimum left ventricular dimension to A_2. This interval was taken as positive when the minimum left ventricular dimension preceded, and negative when it followed, A_2.

(3) The time interval from the minimum left ventricular dimension to the onset of mitral valve opening.

(4) The change in left ventricular dimension during the period of inscription of the upstroke of the apex cardiogram expressed as a percentage of the total dimensional change during the cardiac cycle.

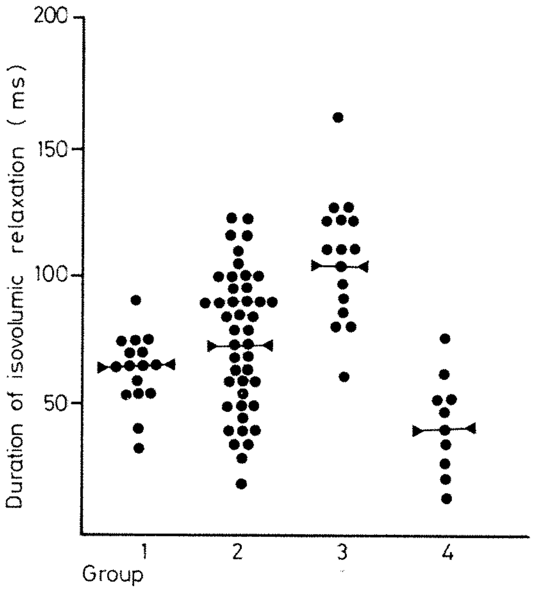

Fig. 2 *Duration of isovolumic relaxation in normal subjects (group 1), patients with coronary artery disease (group 2), hypertension (group 3), and mitral stenosis (group 4). Mean values for each group are indicated.*

Results

(1) ISOVOLUMIC RELAXATION TIME

Isovolumic relaxation times are shown in Fig. 2. (Here and subsequently in this paper mean values are followed by ± 1 standard deviation.) In normal subjects, the mean was 65 ± 15 ms. RR interval was positively correlated with isovolumic relaxation time in normal subjects, the regression equation being:

$$\text{IVR} = 0{\cdot}041\ (\text{RR interval}) + 27\ \text{ms},\ r = 0{\cdot}48,\ P < 0{\cdot}001.$$

The slope of the regression equation differed significantly from unity, and the intercept from zero ($P < 0{\cdot}01$ for each). Since the correlation coefficient was low, no attempt was made to use this regression equation as the basis for any 'correction' procedure to allow for the effect of heart rate. In patients with hypertension, isovolumic relaxation time was significantly prolonged to a mean of 105 ± 25 ms ($P < 0{\cdot}001$), and in those with mitral stenosis, it was shortened to a mean of 40 ± 20 ms ($P < 0{\cdot}01$. In patients with ischaemic heart disease, the mean value was increased to 75 ± 25 ms ($P < 0{\cdot}05$). Results from individual patients are shown in Fig. 2.

(2) TIMING OF AORTIC VALVE CLOSURE (Fig. 3)

In normal subjects, aortic valve closure invariably preceded the mimimum left ventricular dimension by a mean of 40 ± 10 ms, so that there was a further reduction in dimension of 2 ± 1 mm during isovolumic relaxation. By contrast, in patients with coronary artery disease, aortic valve closure was either synchronous with or even followed the minimum left ventricular dimension, which therefore increased rather than diminished during the period of isovolumic relaxation. Though the spread of values was large in the group of patients with hypertension, aortic valve closure preceded the minimum left ventricular dimension by a mean of 25 ± 30 ms, a value not significantly different from normal. In those with mitral stenosis, however, it was significantly delayed, so that its mean timing followed the minimum left ventricular dimension by 30 ± 35 ms.

(3) RELATION OF DELAY IN A_2 TO INCOORDINATE CONTRACTION

Patients with coronary artery disease were investigated in greater detail in order to see whether a delay in aortic valve closure could be related to incoordinate left ventricular contraction. This was studied using the relation between the left ventricular dimension and the apex cardiogram, since a reduction of the dimension by more than 15 per cent during the upstroke of the apex cardiogram correlates closely with abnormal outward wall movement during early systole shown by angiography (Doran *et al.*, 1978). The results are given in Table 1 which shows that when incoordinate contraction thus identified is present, there is a much greater tendency for aortic valve closure to be delayed than when it is absent ($P < 0{\cdot}001$).

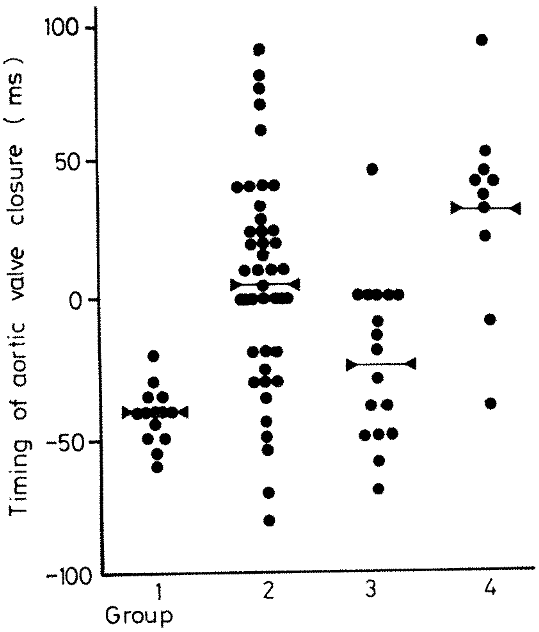

Fig. 3 *Time of aortic valve closure with respect to minimum left ventricular dimension in normal subjects (group 1), patients with coronary artery disease (group 2), hypertension (group 3), and mitral stenosis (group 4). Positive time intervals indicate that aortic valve closure follows minimum left ventricular dimension. Mean values for each group are indicated.*

Table 1 *Relation between timing of aortic valve closure and isovolumic contraction in patients with coronary artery disease ($P < 0{\cdot}001$, Fisher exact probability test)*

	Co-ordinate isovolumic contraction	*Incoordinate isovolumic contraction*
Normal timing of aortic valve closure	10	3
Delayed aortic valve closure	2	24

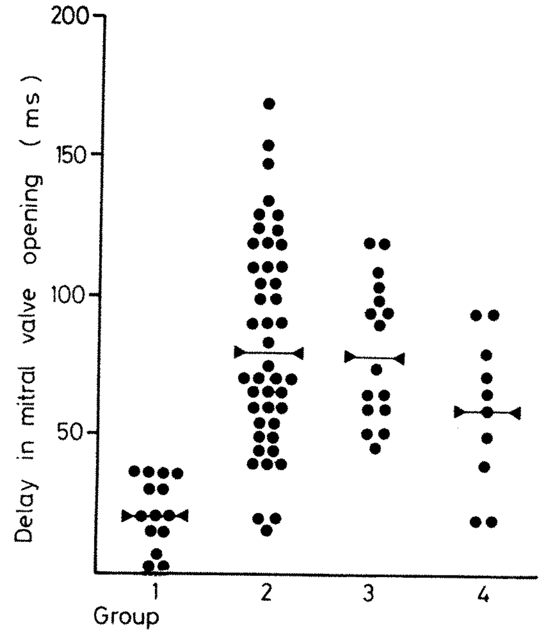

Fig. 4 *Time of mitral valve opening with respect to minimum left ventricular dimension in normal subjects (group 1), patients with coronary artery disease (group 2), hypertension (group 3), and mitral stenosis (group 4). Mean values for each group are indicated.*

(4) TIMING OF MITRAL VALVE OPENING (Fig. 4)

In normal subjects, mitral valve opening, taken as the time of separation of the two cusps, occurred at a mean of 20 ± 10 ms after minimum left ventricular dimension. The relation of the timing of mitral valve opening to aortic valve closure is shown in Table 2. When aortic valve closure was delayed, mitral valve opening was invariably delayed too. In 13 patients the timing of aortic valve closure was normal: 6 showed normal timing of mitral valve opening and 7 delayed opening ($\chi^2 = 12{\cdot}9$, $P < 0{\cdot}001$). However, in patients with coronary artery disease there was no relation between delay in aortic valve closure and the duration of isovolumic relaxation ($\chi^2 = 0{\cdot}13$), indicating that these were independently variable, both late aortic valve closure and prolonged isovolumic relaxation time contributing separately to delay mitral valve opening.

Table 2 *Relation between timing of aortic valve closure and mitral valve opening in patients with coronary artery disease* ($\chi^2 = 12{\cdot}9$, $P < 0{\cdot}001$)

	Normal timing of mitral valve opening	*Delayed mitral valve opening*
Normal timing of aortic valve closure	6	7
Delayed aortic valve closure	0	31

In patients with hypertension, mitral valve opening was significantly delayed by a mean of 80 ± 25 ms ($P < 0{\cdot}001$), with values for 11 of the 16 patients lying outside the 95 per cent confidence limits of normal. Since the timing of aortic valve closure was normal in these patients, the dominant mechanism of delay in mitral valve opening was prolongation of isovolumic relaxation.

In patients with mitral stenosis, mitral valve opening was delayed by a mean of 60 ± 35 ms, significantly different from normal ($P < 0{\cdot}01$). Since isovolumic relaxation was abnormally short in these patients, this indicates that delayed aortic valve closure can coexist with a reduced isovolumic relaxation period.

Discussion

The clinical investigation of left ventricular function has traditionally proceeded along two different lines. The first approach was originally formalised by Wiggers (1921) and depends upon the measurement of time intervals between well-defined events in the cardiac cycle, usually determined by valve movement. The second, direct observation of left ventricular wall movement, was made possible by angiography, and later by echocardiography. The relation between these two approaches, in essence, is the relation between valvar and endocardial movement, but this has not been well defined. In the present paper, therefore, to this end, we investigated events during late systole and early diastole in order to clarify them in greater detail.

Although there has been controversy as to the exact mechanism of the genesis of the second heart sound (Chandraratna *et al.*, 1975; Anastassiades *et al.*, 1976) there is no doubt that the first high frequency vibration of the aortic component is synchronous with aortic valve closure shown by echocardiography (Leatham and Leech, 1975; Rodbard and Matthews, 1975) and with the dicrotic notch of the high fidelity aortic root pressure trace (Hirschfield *et al.*, 1977). We feel justified, therefore, in taking A2 as the start of isovolumic relaxation. There is, however, more doubt as to its end. Some authors (Pohost *et al.*, 1975; Rubenstein *et al.*, 1975; Shiina *et al.*, 1976) have suggested the use of the D′ point on the mitral echogram to indicate the onset of mitral valve opening, but we found this difficult to recognise unambiguously in many patients and, as it occurs approximately 20 ms after the cross-over point of left atrial and left ventricular pressures, did not consider it a satisfactory marker of the onset of left ventricular filling. However, studies in dogs (Laniado *et al.*, 1975) have shown that the onset of blood flow across the mitral valve is synchronous with the initial separation of the cusps and since this can nearly always be observed in man, we have used it as an indicator of the onset of mitral valve opening. It follows the onset of forward movement of the anterior cusp, and thus occurs slightly after, rather than at the same time as minimum left ventricular dimension (Upton *et al.*, 1976). We appreciate that separation of the two cusps may not occur at exactly the same time in different parts of the valve, and that movement of the leaflets into the cavity of the left ventricle during isovolumic relaxation, before actual separation, may allow outward wall movement, but we believe these effects are of small importance and do not invalidate our main conclusions.

In normal subjects and in those with hypertension, aortic valve closure was found to precede the point of minimum left ventricular dimension by a mean of approximately 40 ms. However, in patients with coronary artery disease, it was delayed, the mean for the group having a timing synchronous with that of minimum left ventricular dimension. This delay was strongly correlated with the presence of incoordinate left ventricular contraction. In normal subjects, changes in left ventricular dimension reflect those in the cavity as a whole (Upton and Gibson, 1978), but in patients with coronary artery disease, this generalisation cannot be assumed to apply. This is particularly so when an abnormal reduction in dimension occurs during isovolumic contraction, indicating the presence of aneurysmal movement elsewhere in the cavity. Angiographic studies have shown that regions with such outward wall movement early in systole have delayed or abnormal wall movement throughout ejection (Gibson *et al.*, 1978), with inward wall movement frequently continuing into the period of isovolumic relaxation. Tension persisting in such areas might be expected to delay the fall in ventricular pressure and thus to alter the timing of aortic valve closure with respect to the normal region of the cavity studied by the echocardiographic dimension. The strong correlation between isovolumic contraction abnormalities and delayed aortic valve closure appears to provide evidence in favour of this hypothesis. The normal timing of aortic valve closure in patients with hypertension suggests that in them this mechanism does not apply, and that systolic wall movement is co-ordinate. We are unable to provide a satisfactory explanation for the delay in aortic valve closure in mitral stenosis, though it may be related to the inferobasal abnormality of left ventricular wall movement described by Heller and Carleton (1970).

Isovolumic relaxation time was approximately 65 ms in normal subjects, appreciably lower than that previously described by Benchimol and Ellis (1967). However, their measurements were obtained using the 'O' point of the apex cardiogram, which has subsequently been shown to follow mitral valve opening by a time interval of up to 120 ms (Friedman, 1970; Prewitt *et al.*, 1975). Values obtained in the present study were similar to those reported by Sahn (1977) in children, using a double echo method, allowing aortic valve closure to be observed directly. Prolongation of isovolumic relaxation time was common in patients with hypertension, and not explicable on the basis of heart rate. In them it was this prolongation of isovolumic relaxation, rather than incoordinate systole which was the main cause of delayed mitral valve opening, and apparently resulted from a primary disorder of relaxation. This is compatible with the reduction in the peak rate of left ventricular dimension and prolongation of the rapid filling period previously described in patients with secondary left ventricular hypertrophy (Gibson *et al.*, 1979). Prolongation of isovolumic relaxation time was also seen in approximately one-quarter of the patients with coronary artery disease, a rather lower proportion than that reported by Rubenstein *et al.* (1973). This prolongation was independent of incoordinate systolic function, though both processes combined to delay mitral valve opening with respect to the timing of the minimum left ventricular dimension. We have no direct evidence as to the mechanism for the shortened isovolumic relaxation time in patients with mitral stenosis, but it can be readily explained on simple mechanical grounds as a result of a raised left atrial pressure.

Our results indicate that study of the period of isovolumic relaxation may be of clinical interest, not only with respect to its duration, but also in relation to left ventricular wall movement. Even when isovolumic relaxation time is normal, delay in its onset appears to be strong evidence of segmental abnormality of left ventricular systolic function, indicating that the methods described here may be extended to detect incoordinate cardiac action during ejection as well as during the two isovolumic periods. These observations also clearly differentiate between the abnormal ventricular wall movement seen in early diastole in coronary artery disease and that in hypertension, at the same time underlining the significance of delay in mitral valve opening with respect to the minimum left ventricular dimension.

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Age, sex, and ischaemic heart disease as prognostic indicators in long-term cardiac pacing

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SUMMARY The influence of age, sex, and overt ischaemic heart disease on survival after pacing was studied in a population of 427 patients. The median survival for the whole group was 7·75 years. Women between 55 and 74 years and men between 65 and 74 years enjoyed median survivals in excess of 10 years. Patients over 74 years and men with ischaemic heart disease had median survivals of the order of 5 years and 3½ years, respectively. The findings may help to match generator lifetimes to patient-survival prospects.

The advent of long-life pulse generators coincided with increased awareness of the need for economic use of resources and suggested the need to identify patients whose prognosis for survival may make them unsuitable candidates for the more expensive units. A study of the patients paced at this centre over a 10-year period was therefore undertaken, the principal objectives being the assessment of effects on survival of characteristics readily identifiable at the time when a decision on choice of generator has to be made.

Patients and methods

The 427 patients, in whom permanent endocardial pacing systems were first implanted between 1 September 1967 and 31 August 1977, form the basis of the study. Their age and sex distribution is shown in Table 1. The youngest patient was 6 years old at the time of implantation and the oldest 92. None had life-threatening extracardiac disease. Fifty-seven of the men and 33 women had ischaemic heart disease as evidenced by a clear history of angina pectoris and/or myocardial infarction. Inadequate numbers or insufficiently reliable data precluded interest in other characteristics which might have influenced survival.

Table 1 *Age and sex distribution of patients*

Age (y)	*Men*	*Women*
<55	19	19
55-64	51	29
65-74	94	62
>74	71	82
Total	235	192

Asynchronous pacemaker systems were used routinely until 1972 (75 patients) but since then it has been standard practice to install venticular-inhibited ('demand') generators and only 21 patients received 'fixed-rate' units at first implantation. Many were subsequently converted to 'demand' pacing but 44 retained asynchronous systems until the end of the study. The indications for pacing were symptomatic complete heart block or sinuatrial disorder (26 patients).

Patients were seen for follow-up at intervals of 6 months or less. When patients could not attend one of the pacing clinics held throughout the Region, they were visited at home by technicians. For the purposes of this study, the end-point was the date of the last technical check or of death. The cause of death was sought from necropsy reports or from the last known medical attendant.

Life tables were compiled by the method of Peto *et al.* (1977).

Results

One hundred and two patients died (36 women and 66 men). Four of these (0·9% of those paced) died in the immediate postoperative period. The cause of death was ascertained in 46 other instances; in 37 it was cardiovascular (acute myocardial infarction in 14, congestive failure in 12) and in 5 it was neoplastic. In only 5 was there considered to be a possibility

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Table 2 *Median survival in years*

Age at implantation	*Men*	*Women*
< 55	> 10	7·5
55-64	6·5	> 10
65-74	> 10	> 10
> 74	4·75	5
Total	7·5	9

that pacemaker malfunction or competition was involved.

Table 2 shows the median survival, by age and sex, after first implantation of a permanent pacing system. Only those over the age of 74 years proved to enjoy a median survival of less than 6 years. Fig. 1 depicts the results of life-table analysis of the whole study group. Their survival is not significantly different from that of the age- and sex-matched East Anglian population in general (Registrar General, 1973). However, those under 55 years at the time of implantation of the first pacemaker system fared worse ($P < 0{\cdot}001$) as did men in the 55 to 64 years age-group ($P < 0{\cdot}001$). Fig. 2 shows the different survival experience of the sexes, women with pacemakers faring better than men ($P < 0{\cdot}05$). Fig. 3 shows the poorer survival of those with ischaemic heart disease, compared with those not known to have it ($P < 0{\cdot}001$). The median survival of women in this group was 7·5 years but of men only 3·5 years. Table 3 summarises the significant differences found in relative death rates between the subgroups and matched East Anglian populations.

Discussion

The median survival, for the whole study group, of 7·75 years is in line with reported experience of patients paced for heart block (Sowton and Flores, 1971; Simon, 1976; Stoney *et al.*, 1977) and sug-

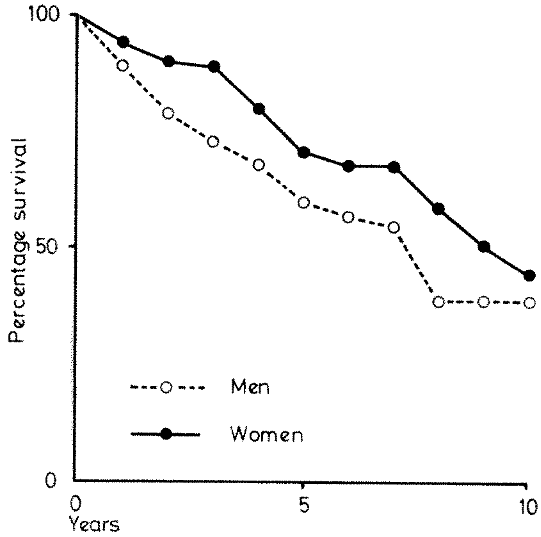

Fig. 2 *Comparative survival of the men and women with pacemakers.*

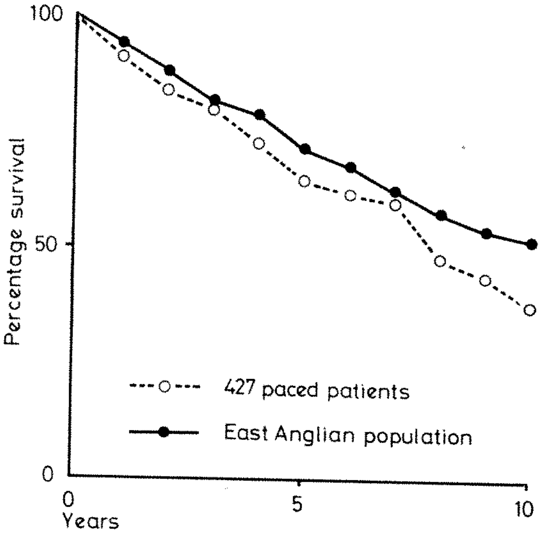

Fig. 1 *Survival, by life-table analysis, of the 427 'paced' patients compared with that of an age and sex matched East Anglian population.*

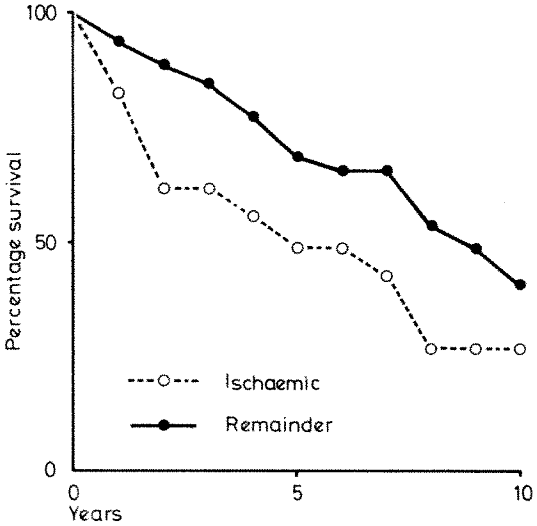

Fig. 3 *Comparative survival of those with ischaemic heart disease and the remainder of the study population.*

Table 3 *Relative death rates of paced subgroups and comparable East Anglian population* (= *l*)

Compared groups		*Relative death rates*		*P*
Men (paced)	Women (paced)	1·24	0·74	< 0·05
< 55 (y) (paced)	East Anglian population	11·42	1	< 0·001
Men 55-64 (y) (paced)	East Anglian population	4·54	1	< 0·001
All ischaemic group (paced)	Remainder of group (paced)	1·88	0·80	< ·0001
Male ischaemic group (paced)	Remainder of male group (paced)	1·83	0·79	< 0·001
Female ischaemic group (paced)	Remainder of female group (paced)	1·97	0·85	< 0·05

gests an improvement on the natural prognosis (Cosby *et al.*, 1966; Edhag and Swahn, 1976). The inclusion of some patients (6% of those paced) with sinuatrial disorder is unlikely to have improved the prognosis of the study group as a whole (Wohl *et al.*, 1976; Shaw *et al.*, 1978). Neither is the initial use of asynchronous generators likely to have had a statistically significant effect on survival (Siddons, 1974) though 'demand' systems are now preferred because of the frequency of emergent, potentially competitive, rhythms even in those apparently in stable, complete heart block at the time of generator implantation (Grover *et al.*, 1974; Furman and Fisher, 1977).

In contrast with the findings of Amikam *et al.* (1976), this study indicates a better than average prognosis for women paced after the age of 54 years. The poorer (than normal) survival of the younger patients, and of men in the 55 to 64 year age group, may be the result of the common association of coronary artery disease with atrioventricular block in middle age (Ginks *et al.*, 1978). The relatively good survival of the elderly is confirmed (Amikam *et al.*, 1976; Rettig *et al.*, 1977). A poor 10-year survival for those over 74 years (Stoney *et al.*, 1977) is not surprising as only 50 per cent of a normal equivalent population may be expected to survive for 6 years.

In this study, patients over 74 years comprised one of only two subgroups of patients with median survival periods of less than 6 years after first (permanent) pacing. The other was the group of men with overt ischaemic heart disease. These findings accord with those of Simon and Zloto (1978) who were also able to identify hypertensive heart disease and congestive failure as indicators of a poorer prognosis. The malign significance of heart failure has recently been highlighted by Hetzel *et al.* (1978).

Patients free from these stigmata, and under 75 years of age, might now reasonably be regarded as candidates for truly long-life pulse generators on both economic (Norman, 1976) and other grounds. For those with more limited survival prospects—nevertheless often of the order of 3 to 5 years in group median terms—less expensive generators with matched potential life-spans may be preferred.

We thank Mr Leslie Daly of the Department of Social and Preventive Medicine, University College, Dublin 4, for his help with the statistical analysis.

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British Heart Journal, 1979, **42**, 61-64

Waller—pioneer of electrocardiography

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In the history of electrocardiography, Einthoven dominates the published papers, and the contribution of A. D. Waller, who first recorded the electrocardiogram in man with surface electrodes (Waller, 1887; Einthoven, 1912), is often ignored. This is an omission which ought to be remedied.

Augustus Desiré Waller used his full name in order to distinguish himself from his eminent father, Augustus Volney Waller, remembered for his work on nerve degeneration. Waller senior worked in Paris and his son was born in 1856 and educated there until his father's death in 1870. The widow and son then moved to Scotland and he studied medicine in Aberdeen and Edinburgh. Following his father's interest in physiology, he took an appointment in 1883 as lecturer at the School of Medicine for Women in London and, the following year, was also appointed lecturer in physiology at St Mary's Hospital, Paddington. He married one of his students, the daughter of Sir George Palmer (of Huntley and Palmer biscuit fame), and was greeted at his next St Mary's lecture by a blackboard inscribed 'Waller takes the biscuit'. With characteristic humour, Waller added 'and the tin as well'.

At St Mary's his laboratory in the original medical school has changed function many times, but the building still stands, and adjacent to his area is the newly named Waller Cardio Pulmonary Unit. In 1887 he started work on the electrical activity of the heart which was already well known from studies on the exposed heart, but he sought to demonstrate cardiac potentials from the limbs of intact animals and from man. This experiment was successful and it was published in the *Journal of Physiology* (Waller, 1887); in this he described the use of the Lippman capillary electrometer to record the first 'electrogram' from both animals and man. In the paper of 1887, surface electrodes were strapped to the front and back of the chest, and in a paper of 1888, he used saline jars in which the extremities were immersed. A light beam interrupted by the mercury column of the Lippman electrometer enabled photographic records to be made on plates mounted on slowly moving toy train wagons (Fig. 1, 2, and 3).

In his address in 1888 he elaborated on his studies which also proved that contraction of the heart was not a simultaneous process but showed initiation at the apex and termination at the base.

In an informal address at St Mary's in 1915, Waller reminisced about his pioneer work. 'I studied the hearts of all sorts of animals . . . and one fine day after leading off from the exposed heart of a decapitated cat to study the cardiogram by aid of a Lippman electrometer, it occurred to me that it ought to be possible to use the limbs as electrodes and thus lead off from the heart to the electrometer without exposing the heart, i.e. from the intact and normal organ. Obviously man was the most convenient animal to use so I dipped my right hand and left foot into a couple of basins of salt solution, which were connected with the two poles of the electrometer and at once had the pleasure of seeing the mercury column pulsate with the pulsation of the heart. . . . This first demonstration was made in St Mary's laboratory in May 1887 and demonstrated there to many physiologists and among others, to my friend Professor Einthoven of Leiden. . . . During the summer of that year, I made a complete survey of all sorts of leads from the hands and feet and mouth!'

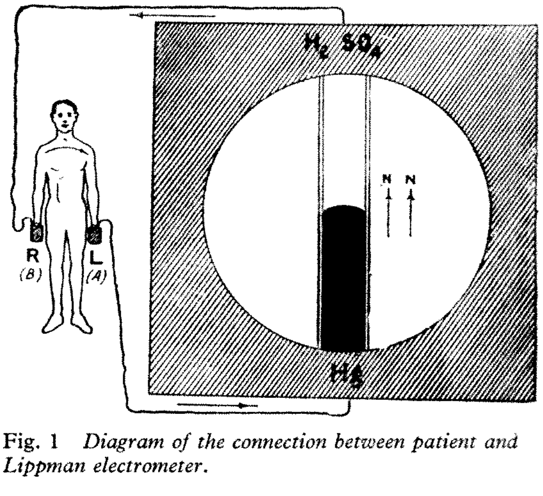

Fig. 1 *Diagram of the connection between patient and Lippman electrometer.*

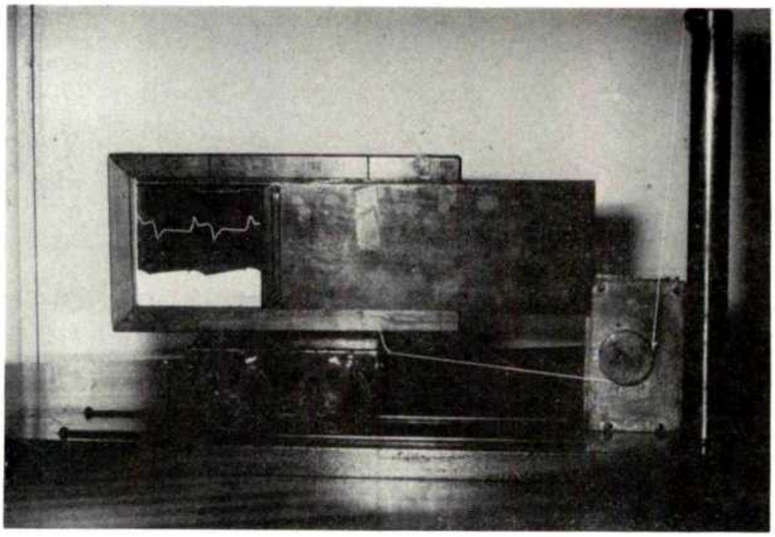

Fig. 2 *Toy train wagon carrying photographic plate.*

These studies were demonstrated before the Royal Society who soon made him a Fellow at the early age of 35.

The capillary electrometer could be used to demonstrate the electrical activity of the heart, but the response of the instrument was too slow for further analysis and useful clinical records were only achieved with the development of the quartz fibre galvanometer (see the historical papers in the *Journal of Physiology*: Adrian *et al.*, 1976; Besterman *et al.*, 1976; Campbell and Pelli, 1976).

In 1903 Waller became professor at the newly founded Physiological Laboratory of the University of London housed in the Imperial Institute, and shortly afterwards became one of the first two consulting physicians to the National Hospital for Diseases of the Heart where he employed the Einthoven string galvanometer electrocardiography extensively.

After Waller's death, Sir Thomas Lewis wrote (Cope, 1973) of him, 'His early work on electrophysiology was extensive, thorough and is well known. He was the first to obtain a human electrocardiogram; this has been the main, though by no means his sole contribution to the science of experimental machines. The discovery long preceded the introduction of the string galvanometer and was the more remarkable in that it was accomplished in the eighties'. Einthoven (1912) himself credited Waller with the first electrocardiogram.

We have been unable to trace any descendants of Waller alive today but his daughter was professor of physics at the Royal Free Hospital Medical School and first drew the attention of one of us (EB) to the apparent neglect of her father, which she amplified in a letter to the *British Medical Journal* (Waller, 1950). In this, she quoted from Sir Thomas Lewis who stated that Einthoven credited Waller with the

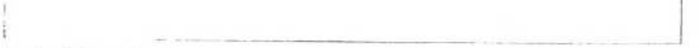

Fig. 3 *Recording from man with time scale at top, pulse tracing in centre, and electrogram at bottom.*

Fig. 1. Man. Heart led off to electrometer from front and back of chest (front to Hg; back to H_2SO_4).

e.e. electrometer. *h.h.* cardiograph. *t.t.* time in seconds.

From *Journal of Physiology* (1887), **8,** 229.

first use of the term electrocardiogram, and also gave a third valuable reference to Waller's original address at St Mary's Hospital Medical School, from the *British Medical Journal* of 1888. One of Waller's sisters, Camelia, emigrated to New Zealand with her husband William Edwards. A female descendant, Dorothy Perry, subsequently married Dr A. C. Hayton of New Plymouth, New Zealand, who has records of a visit by Waller to Auckland in 1914, together with various Walleriana, and is still searching for details of Waller's forebears.

Apart from his cardiographic interest, Waller published a textbook in 1891 *An Introduction to Human Physiology*, a comprehensive work of over 600 pages. In addition, in a different field, he first tried to measure anaesthetic gases used in operations with special reference to chloroform, following several deaths from its use, and his experimental apparatus for this is still in Professor Cresse's department; his cardiographic recordings, toy trains, etc., are housed in the Waller Cardio Pulmonary Unit.

Our scant knowledge of Waller (Fig. 4) as a person is derived, in part, from Professor Halliburton's obituary for the Royal Society, and this is but rudimentary: 'He was short in stature with an "intelligent" face and small pointed yellow beard. His voice was clear and slow. He lectured from October to December and confined his subjects to muscle and nerve'. The other reminiscence by Robert Marshall suggested a certain unconventionality: 'Waller presented a very different appearance from that of our physicians, who were always soberly garbed in frock coats or morning coats and silk hats. He was a short stocky man, very light on his feet. His grey beard and double-breasted blue jacket make him look exactly like a skipper in the Merchant Navy. Like Sir Winston, he seemed to be habitually smoking cigars, and was invariably followed by his bulldog, Jimmy, who also had a Churchillian quality and had the distinction of having had a question asked about him in the House of Commons:

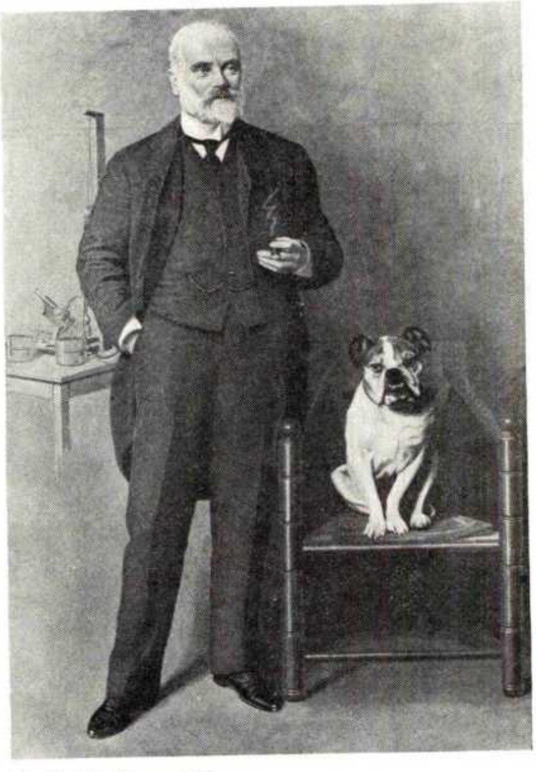

Fig. 4 *Waller and Jimmy.*

Q. 'At a conversazione of the Royal Society at Burlington House on May 12th last, a bulldog was cruelly treated when a leather strap with sharp nails was wound around his neck and his feet were immersed in glass jars containing salts in solution, and the jars in turn were connected with wires to galvanometers. Such a cruel procedure should surely be dealt with under the "Cruelty to Animals Act" of 1876?'

A. 'The dog in question wore a leather collar ornamented with brass studs, and he was placed to stand in water to which some sodium chloride had been added, or in other words, common salt. If my honourable friend had ever paddled in the sea, he will appreciate fully the sensation obtained thereby from this simple pleasurable experience!'

Waller was also renowned for his unfailing success in demonstrations and public experiments, to the delight of his students. He was treasurer of the Physiological Society for 25 years, and he was in the chair in 1890 when the committee resolved not to have a president. One of his interests outside work was motoring, and he was an early devotee of the car. On fairly frequent trips to Paris, he shipped his car from Southampton to Le Havre to enjoy the drive to the French capital.

He lived in St John's Wood where he maintained a small laboratory in which his ever interested wife assisted him in most of his work. Her death probably contributed to his, which occurred shortly afterwards.

He died on 11 March 1922 after two strokes. He left three sons and a daughter, all unmarried, and no direct descendants can be found. In 1924 Einthoven was awarded the Nobel Prize for Medicine. Waller had died in 1922 and so would not have been eligible for a joint award.

The late Sir Zachary Cope was responsible for the initiative to commemorate Waller in St Mary's. This has taken the form of a permanent display of his recordings and apparatus in the unit named after him. We also echo Sir Zachary's sentiments that the omission of Waller's name from the Dictionary of National Biography is inexplicable.

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British Heart Journal, 1979, **42**, 65-73

Effects of acute changes in systemic arterial pressure on left ventricular diastolic stiffness and mass[1]

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SUMMARY Acute interventions may shift the left ventricular diastolic pressure-volume curve in man, but the mechanism is unclear. Methoxamine hydrochloride was given to 7 patients without coronary disease to raise mean arterial pressure 25 to 35 mmHg. High fidelity left ventricular pressures were recorded simultaneously with single plane cine left ventriculography and pressure-volume curves were constructed before and during methoxamine infusion. Methoxamine significantly increased left ventricular end-diastolic pressure (12 ± 1 vs 25 ± 1 mmHg), left ventricular minimal diastolic pressure (6 ± 1 vs 15 ± 2 mmHg), right atrial pressure (5 ± 1 vs 9 ± 1 mmHg), left ventricular end-diastolic volume (185 ± 32 vs 207 ± 37 ml), left ventricular end-systolic volume (72 ± 19 vs 93 ± 25 ml), and left ventricular mass (168 ± 17 vs 187 ± 18 g), while left ventricular wall thickness changed little (8·5 ± 0·6 vs 8·7 ± 0·5 mm). In each patient the diastolic pressure-volume curve was shifted upward, with left ventricular pressure being higher for any given volume with methoxamine. Serial ventriculograms in 5 subjects who did not receive methoxamine showed no shift. Since methoxamine has no effect on the myocardium and since the subjects had no evidence of left ventricular ischaemia, it is unlikely that the changes in the pressure-volume curve are caused by intrinsic changes in myocardial properties. Viscous properties cannot solely account for the observations, since the diastolic filling rate was altered only in the first one-third of diastole. The increase in left ventricular wall mass suggests that acute increases in systemic arterial pressure may augment left ventricular stiffness by coronary vascular engorgement and an erectile effect on the myocardium. The study cannot exclude pericardial restriction and changes in right ventricular loading as contributing factors in acute shifts in the left ventricular diastolic pressure-volume curve.

Recently, it has been recognised that acute interventions may alter the relation between left ventricular diastolic pressure and volume in man. Patients with coronary artery disease who develop angina may shift the pressure-volume curve upward so that, at a given volume, pressures are higher during angina (Barry *et al.*, 1974; Flessas *et al.*, 1976; Mann *et al.*, 1977); and patients with congestive heart failure or coronary artery disease may shift the pressure-volume curve downward with nitroprusside or glyceryl trinitrate so that, at a given volume, pressures are lower during vasodilator therapy (Alderman and Glantz, 1976; Parmley *et al.*, 1976; Brodie *et al.*, 1977). It is not clear whether these shifts are the result of intrinsic changes in myocardial properties or the result of changes in one or more of the extrinsic constraints to left ventricular filling, such as right ventricular loading, pericardial restriction, or coronary artery perfusion pressure. The present study was designed to help clarify the potential role of these extramyocardial factors in acute changes in the diastolic pressure-volume relation. Pharmacological intervention with methoxamine hydrochloride was chosen because this drug acts selectively to increase systemic vascular resistance and systemic arterial pressure with little or no effect on the myocardium (Eckstein and Abboud, 1962). The results indicate that acute rises in systemic arterial pressure increase left ventricular wall mass and diastolic stiffness and suggest that this may be the result of coronary vascular engorgement and an erectile effect on the myocardium.

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Table *Haemodynamic and angiographic data before and during methoxamine infusion*

Case no.	*Diagnosis*	*CI (l/min per m²)*	*HR (b/min)*	*SVR (dynes s cm⁻⁵)*	*SA (mmHg)*	*RA (mmHg)*	*LVEDP (mmHg)*	*LVMDP (mmHg)*	*+dP/dt (mmHg/s)*	*−dP/dt (mmHg/s)*
1	CPNC	C 3·7	85	1482	115	2	14	4	1400	1533
		M 3·6	83	1853	145	6	22	12	1633	2433
2	CM	C 3·6	65	1045	105	7	15	9	800	1200
		M 3·9	77	1185	130	10	26	17	1200	1200
3	CPNC	C 2·8	84	1745	100	4	13	5	—	—
		M 3·1	78	2054	127	6	26	8	—	—
4	CPNC	C 2·3	98	836	93	1	8	3	1020	1200
		M 2·6	103	2007	135	7	30	21	1620	1980
5	CPNC	C 4·2	85	834	105	6	11	6	2520	2590
		M 4·5	81	1127	150	10	26	13	3150	3500
6	CPNC	C 3·4	78	1059	100	6	11	7	1143	1714
		M 3·5	78	1424	140	10	25	11	1314	2057
7	CPNC, SSS	C 1·4	77	3319	118	6	14	8	—	—
		M 1·4	77	3685	140	11	25	22	—	—
Mean ± SEM		C 3·1 ± 0·4	82 ± 4	1474 ± 333	105 ± 9	5 ± 1	12 ± 1	6 ± 1	1376 ± 302	1647 ± 256
		M 3·2 ± 0·4	82 ± 4	1905 ± 329	138 ± 3	9 ± 1	25 ± 1	15 ± 2	1783 ± 352	2234 ± 375
t value		2·66	0·31	3·39	9·53	8·20	8·02	4·37	4·37	3·27
P		< 0·05	NS	< 0·02	< 0·001	< 0·001	< 0·001	< 0·005	< 0·005	< 0·02

CPNC, chest pain with normal coronary angiography; CM, cardiomyopathy; SSS, sick sinus syndrome; CI, cardiac index; HR, heart rate; S systemic vascular resistance; SA, mean arterial pressure; RA, mean right atrial pressure; LVEDP, left ventricular end-diastolic pressure; LVM left ventricular minimal diastolic pressure; +dP/dt, peak positive dP/dt; −dP/dt, peak negative dP/dt; EDV, left ventricular end-diastolic volu ESV, left ventricular end-systolic volume; SV, angiographic stroke volume; EF, ejection fraction; Mass, left ventricular mass; DFR_1 diastolic fill rate in first 1/3 of diastole; DFR_2, diastolic filling rate in middle 1/3 of diastole; DFR_3, diastolic filling rate in last 1/3 of diastole; DFR_T, diastolic fill rate for diastole as a whole; C, control; M, methoxamine.

Methods

PATIENTS

Patients with chest pain but without objective clinical evidence of ischaemic heart disease who were scheduled for routine diagnostic cardiac catheterisation at North Carolina Memorial Hospital were invited to participate in the study. The experimental procedure was approved by the Hospital Committee on the Rights of Human Subjects, and informed consent was obtained from each patient. Patients with significant coronary artery obstructions by angiography, mitral valve prolapse, or hypertrophic cardiomyopathy were excluded from the study. The study group thus consisted of 7 patients (Table). Five patients had chest pain syndromes with normal coronary and left ventricular angiography and normal or nearly normal haemodynamics. One patient (case 2) had haemodynamic and angiographic evidence of a mild congestive cardiomyopathy probably secondary to alcohol, and 1 patient (case 7) had sick sinus syndrome, with a permanent transvenous ventricular demand pacemaker and a low cardiac index. Four patients (cases 1, 5, 6, and 7) had a history of mild hypertension and 3 patients (cases 2, 4, 6) were taking propranolol 80 to 160 mg/day which was discontinued 12 to 36 hours before the procedure.

METHODS AND EQUIPMENT

Cardiac catheterisation was performed in the fasting state using the right brachial arterial approach after premedication with diazepam (Valium, 10 mg po) and atropine sulphate (0·5 mg intravenously). Right heart catheterisation was performed using a Gorlin pacing catheter. Left ventricular pressure was recorded using high fidelity micromanometer tipped catheters (Mikrotip, Millar Instruments, Houston, Texas) in all patients to permit accurate measurement of ventricular pressure simultaneously with the performance of cineangiography. The patients were instructed to avoid deep respirations and the Valsalva manoeuvre during the cineangiogram and recording of pressures. The first derivative of left ventricular pressure (dP/dt) was obtained using a passive (resistance-capacitance) differentiating circuit with a 0·5 ms time constant and an output linearly proportional to the input frequency, within 5 per cent, up to a rated maximal frequency of 75 Hz. Single plane (RAO) left ventricular cineangiography was performed with the injection of 30 to 40 ml of radiographic contrast material (Renografin 76, E. R.

DV nl)	*ESV* (*ml*)	*SV* (*ml*)	*EF*	*LV wall thickness* (*mm*)	*Mass* (*g*)	*DFR$_1$* (*ml/s*)	*DFR$_2$* (*ml/s*)	*DFR$_3$* (*ml/s*)	*DFR$_T$* (*ml/s*)
09	31	78	0·72	8·5	134	278	159	222	200
06	38	68	0·64	9·0	141	277	388	268	290
64	180	184	0·51	7·5	217	786	201	444	465
01	233	168	0·42	7·5	237	815	343	478	549
53	40	113	0·74	6·5	111	254	269	396	314
70	59	111	0·65	7·0	134	407	148	435	343
76	75	101	0·57	8·5	166	416	426	511	467
26	100	126	0·56	8·5	193	1000	167	291	500
58	58	100	0·63	11·5	233	481	241	244	327
59	63	106	0·63	11·5	236	958	361	153	491
04	75	129	0·63	8·5	184	491	296	407	398
41	87	154	0·64	9·0	223	806	644	83	503
29	48	81	0·63	8·5	132	500	95	56	225
36	71	65	0·48	8·5	142	472	78	78	226
35 ± 32	72 ± 19	112 ± 13	0·63 ± 0·03	8·5 ± 0·6	168 ± 17	458 ± 67	241 ± 40	326 ± 60	342 ± 40
07 ± 37	93 ± 25	114 ± 15	0·57 ± 0·03	8·7 ± 0·5	187 ± 18	676 ± 108	304 ± 73	255 ± 60	415 ± 48
3·06	3·35	0·26	2·60	2·12	3·86	2·36	0·80	1·26	3·45
0·025	< 0·02	NS	< 0·05	NS	< 0·01	NS	NS	NS	< 0·02

Squibb & Sons, Inc., Princeton, NJ) into the ventricular chamber at a rate of 10 to 15 ml per second. A Siemens caesium iodide image intensifier was used and cineangiograms were recorded on 35 mm film at 56 frames per second. Care was taken to ensure that neither the patient nor the equipment was moved and that the degree of obliquity was reproduced between sequential RAO angiograms. A movable marker synchronised with the QRS complex of the electrocardiogram was filmed with the cineangiogram and used to identify end-diastole. A recording of the electrocardiogram, high fidelity left ventricular pressure, injection marker, and cineangiographic frame markers was made simultaneously with the cineangiogram, and enabled left ventricular pressures to be matched with left ventricular angiographic silhouettes throughout the cardiac cycle (Fig. 1).

EXPERIMENTAL PROCEDURE

After placement of the catheters, baseline (control) measurements were made of Fick or indicator dilution cardiac output, systemic arterial pressure (SA), right atrial pressure (RA), high fidelity left ventricular pressure, and the first derivative of left ventricular pressure with respect to time (dP/dt). Control left ventricular cineangiography and simultaneous high fidelity left ventricular pressure measurement were then performed. Ten to 15 minutes later, after intracardiac pressures had returned to baseline, methoxamine hydrochloride (Vasoxyl, 100 mg in 500 ml D$_5$W) was infused to raise mean arterial pressure 25 to 35 mmHg, and this state was maintained for 10 minutes. In order to prevent the reflex bradycardia that occurs with methoxamine infusion, the heart was paced at a heart rate approximately equal to the control heart rate with the pacing catheter positioned in the high right atrium. Cardiac output, intracardiac pressure measurements, and left ventricular cineangiography were repeated and methoxamine was then discontinued. In 5 control subjects with chest pain and normal coronary angiography, 2 left ventricular cineangiograms with high fidelity left ventricular pressure measurements were performed 10 to 15 minutes apart, without methoxamine infusion, to assess the effect of the cineangiogram itself on the diastolic pressure-volume relation. The high fidelity left ventricular pressure was balanced with the pressure measured through the fluid-filled lumen of the Millar catheter before and after each cineangiogram to ensure that there was no drift in the high fidelity pressure.

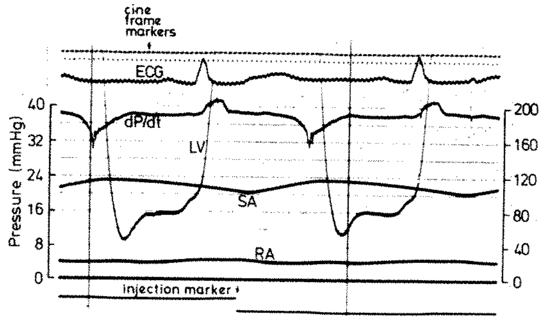

Fig. 1 *Recording of the electrocardiogram (ECG), high fidelity left ventricular pressure (LV), first derivative of left ventricular pressure with respect to time (dP/dt), mean systemic arterial pressure (SA), mean right atrial pressure (RA), injection marker, and cineangiographic frame markers made simultaneously with the left ventricular cineangiogram. The injection marker signals the time at which contrast material is injected into the left ventricular chamber and enables cardiac cycles on the pressure tracing to be matched with corresponding cycles on the cineangiogram. The electrocardiogram and cineangiographic frame markers, combined with a moveable marker synchronised with the QRS complex of the electrocardiogram and recorded on the cineangiogram, enable left ventricular pressures to be matched with left ventricular angiographic silhouettes throughout each cardiac cycle.*

ANALYSIS OF DATA

For each patient, left ventricular angiographic silhouettes were traced every frame (18 ms intervals) from initial diastole, which was defined as the angiographic frame immediately before the mitral valve opening movement, to end-diastole, which was defined as the angiographic frame during which the QRS marker first moved. The earliest adequately visualised beats were used, and the first 2 beats after premature systoles were excluded. High fidelity left ventricular pressures, recorded simultaneously with the cineangiogram, were matched with left ventricular angiographic silhouettes as shown in Fig. 1. Left ventricular volumes were calculated using the area-length method and a grid calibration technique (Kasser and Kennedy, 1969) with the help of a sonic digitiser (Science Assessories Corp., Southport, Conn.) interfaced to a programmable calculator (Wang Laboratories, Inc., Tewksbury, Mass). Interobserver variation in the measurement of volumes by this technique was found to be less than 4 per cent. Pressure-volume curves were constructed throughout diastole for each study patient from data obtained during the control period and during methoxamine infusion. Pressure-volume curves were also constructed for the 5 subjects who had serial angiograms without methoxamine infusion.

Left ventricular wall thickness was measured at end-diastole in the RAO projection (Rackley *et al.*, 1964; Kennedy *et al.*, 1970), and correction for magnification was made using a grid calibration technique. Left ventricular mass was calculated at end-diastole using ellipsoidal formulas assuming uniform left ventricular wall thickness.

Diastolic filling rates were measured as the change in calculated ventricular volume during diastole divided by the time over which this change occurred as determined from the number of cineangiographic frames elapsed. Diastolic filling rates were measured during the first, middle, and last thirds of diastole and for total diastole during both the control state and during methoxamine infusion.

Comparisons of haemodynamic and angiographic indices between the control period and methoxamine infusion were made using a two-tailed paired t test.

Results

The relation between left ventricular diastolic pressure and volume in the control state and during methoxamine infusion for each of the 7 study patients is shown in Fig. 2 and 3. In each subject there was a substantial upward displacement of the

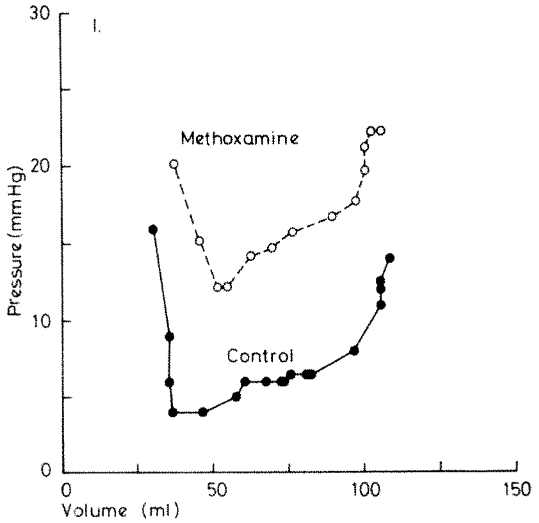

Fig. 2 *Left ventricular diastolic pressure-volume curves before and during methoxamine infusion in a patient with chest pain and normal coronary angiography (case 1, Table). The curve is shifted upward with left ventricular pressure being higher for any given volume with methoxamine.*

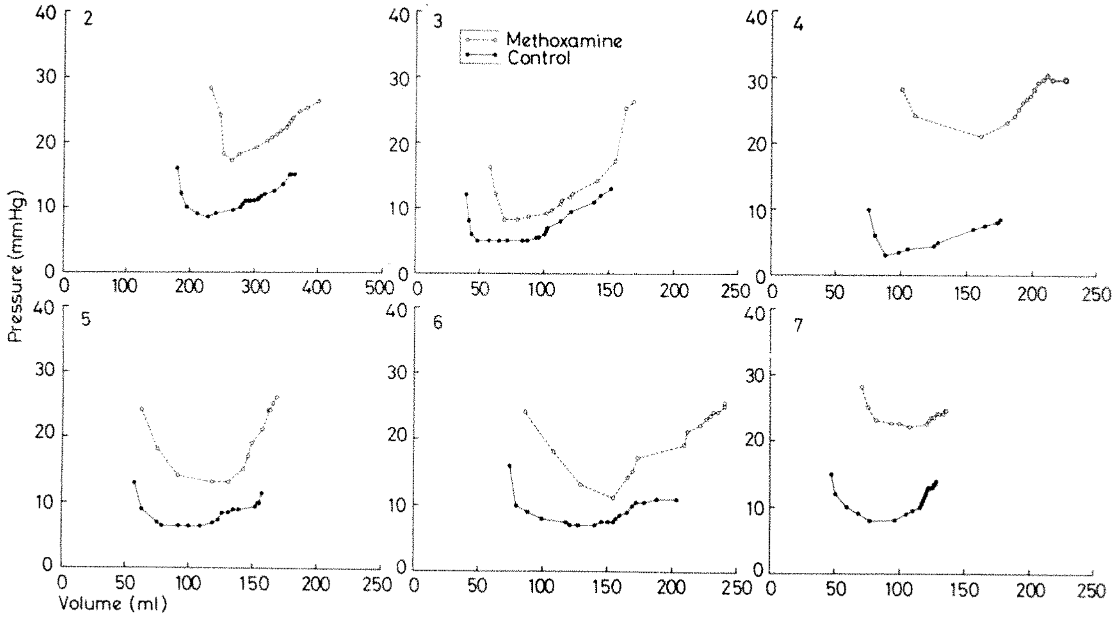

Fig. 3 *Left ventricular diastolic pressure-volume curves in 6 patients with chest with syndromes and normal coronary angiography before and during the administration of methoxamine. In each patient there is a substantial upward displacement of pressure-volume curve with methoxamine. Haemodynamic and ventriculographic data for each patient are shown in the Table.*

pressure-volume curve, so that, at a given volume, pressures were higher during methoxamine infusion. In the 5 subjects who had serial angiography without methoxamine infusion, there was little change in the pressure-volume relation. Data from 3 of these patients are shown in Fig. 4.

The haemodynamic and angiographic data for the 7 subjects are shown in the Table. Systemic vascular resistance and mean arterial pressure increased significantly with methoxamine. Cardiac index increased slightly while heart rate was controlled and did not change. Mean right artial pressure, left ventricular end-diastolic pressure, left ventricular minimal diastolic pressure, peak +dP/dt, and peak −dP/dt all increased significantly. Left ventricular end-diastolic volume and end-systolic

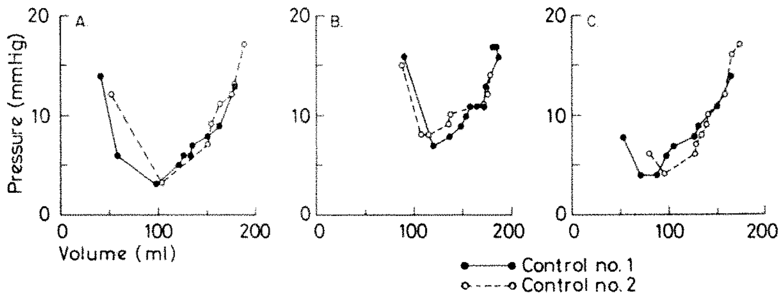

Fig. 4 *Left ventricular diastolic pressure-volume curves in 3 of the 5 patients with chest pain syndromes and normal coronary angiography who underwent serial left ventriculography 15 minutes apart but did not receive methoxamine. In each subject there is no apparent difference between the first and second pressure-volume curves, indicating that ventriculography itself was not responsible for the changes in the diastolic pressure-volume curves seen with methoxamine. (Reproduced with the permission of the* Journal of Clinical Investigation.)

volume increased significantly while stroke volume did not change appreciably and ejection fraction fell slightly. Left ventricular wall thickness at end-diastole increased slightly but not significantly and left ventricular mass increased significantly. The diastolic filling rate increased during the first third of diastole but changed little during the middle and last third of diastole.

The 5 subjects who had serial angiography without methoxamine infusion had no significant change in left ventricular end-diastolic volume (142 ± 14 vs 146 ± 15 ml), wall thickness (7·7 ± 0·9 vs 7·7 ± 0·9 mm), or left ventricular mass (289 ± 41 vs 297 ± 44 g).

Discussion

Methoxamine hydrochloride is an alpha-adrenergic agonist whose predominant effect in experimental animals and man is vasoconstriction (Eckstein and Abboud, 1962). Previous studies in dogs have shown that methoxamine infusion results in an increase in systemic arterial pressure and systemic vascular resistance, a reflex bradycardia mediated primarily through baroreceptors, a fall in cardiac index, and an increase in pulmonary artery and right atrial pressures (Aviado and Wnuck, 1957; Brewster *et al.*, 1960; Eckstein and Abboud, 1962). The drug has no significant inotropic effect on the human or dog heart (Goldberg *et al.*, 1960; Eckstein and Abboud, 1962), though there is some recent evidence that methoxamine may exert a positive inotropic effect in isolated rabbit and cat papillary muscles at low frequencies of stimulation (Endoh and Schumann, 1975; Rabinowitz *et al.*, 1975). The drug has little effect on venous tone (Eckstein and Hamilton, 1957).

In our study systemic arterial pressure and systemic vascular resistance increased significantly while heart rate was controlled with atrial pacing and did not change. Cardiac index increased slightly, which differs from most previous animal studies, and is probably related to the fact that heart rate was controlled. The slight increase in cardiac index in our subjects may be explained by increases in preload, but an increase in contractility cannot be excluded. Peak positive dP/dt increased significantly with methoxamine probably related to increased preload (end-diastolic volume) (Mahler *et al.*, 1975), and peak negative dP/dt increased significantly probably because of increased systemic arterial pressure (Weisfeldt *et al.*, 1974b). Both right atrial and left ventricular diastolic pressures increased substantially. In previous animal studies, increased filling pressures with methoxamine have been attributed to increased left ventricular volumes resulting from compensatory left ventricular dilatation in the face of an increased afterload, but left ventricular volumes have not been measured (Brewster *et al.*, 1960). Our study shows that the increased ventricular diastolic pressures are only partly the result of increased left ventricular volumes. The major factor responsible for the increased left ventricular diastolic pressures with methoxamine is an alteration in the left ventricular diastolic pressure-volume relation.

Acute changes in the left ventricular diastolic pressure-volume relation in man have only been recognised recently and the mechanisms responsible for these changes remain unclear. Several investigators have shown an upward shift in the left ventricular diastolic pressure-volume relation (higher pressure at a given volume) in patients with coronary artery disease who develop angina in response to atrial pacing (Barry *et al.*, 1974; Mann *et al.*, 1977) or isometric hand grip (Flessas *et al.*, 1976). This has been attributed to impaired left ventricular relaxation. There is convincing evidence in experimental animals and man that left ventricular relaxation may be impaired with ischaemia (Tyberg *et al.*, 1970; McLaurin *et al.*, 1973; Weisfeldt *et al.*, 1974a), but whether this impaired relaxation extends throughout diastole to alter the pressure-volume relation in middle and late diastole is uncertain. Studies in open chested dogs during acute global ischaemia while on right heart bypass at constant heart rate and aortic pressure and with the pericardium removed, failed to show any change in the pressure-volume relation (Palacios *et al.*, 1976). This raises the possibility that the acute changes in the pressure-volume relation seen in man may be caused by extramyocardial factors rather than intrinsic changes in myocardial properties. Studies with sodium nitroprusside and glyceryl trinitrate administered to patients with congestive heart failure and coronary artery disease have shown a downward shift in the diastolic pressure-volume relation (lower pressure at a given volume) (Parmley *et al.*, 1976; Brodie *et al.*, 1977). One possible reason for this effect is that vasodilators may exert a direct relaxant effect on ventricular muscle (Brodie *et al.*, 1976, 1977), but an alternative explanation is that these drugs may alter external constraints to left ventricular filling. The studies of Alderman and Glantz in which pressures were measured primarily through fluid-filled catheters showed a shift of the pressure-volume curve with both nitroprusside and angiotensin and support of the latter view (Alderman and Glantz, 1976).

In our study, acute systolic loading with methoxamine resulted in an upward shift of the diastolic pressure-volume curve in each subject. While there are several possible explanations for this shift, the increase in left ventricular wall mass that also occurred in each subject suggests that acute systolic loading and increases in coronary artery perfusion pressure may result in coronary vascular engorgement and an erectile or stiffening effect on the left ventricular myocardium. This possibility is supported by experimental evidence of animals. In the isovolumic canine left ventricle, Salisbury and his co-authors found that increases in coronary artery perfusion pressure increased the left ventricular end-diastolic pressure; they attributed this to stiffening of the myocardium resulting from an erectile effect caused by the sinusoidal nature of the coronary circulation (Salisbury *et al.*, 1960). Likewise, Ahn *et al.* (1977) found a direct effect of coronary artery perfusion pressure on diastolic stiffness and thickness in the rabbit left ventricle, and Gaasch and Bernard (1977) found that acute changes in coronary blood flow altered left ventricular wall thickness The importance of these observations is uncertain because Abel and Reis (1970) and Templeton *et al.* (1972) were unable to show any change in the stiffness of the canine left ventricle with alterations in coronary perfusion pressure and flow. Nevertheless, our data support the observations of Salisbury *et al.*, Ahn *et al.*, and Gaasch and Bernard and suggest that the human myocardium may act like erectile tissue in response to acute changes in systemic arterial pressure.

The main reservation in drawing this conclusion lies in the limitation in the measurement of left ventricular mass from single plane angiography. The assumption of uniform wall thickness is not precisely true. In addition, it is possible that acute changes in ventricular loading may alter the shape of the left ventricle and invalidate some of the assumptions used in the calculation of left ventricular mass from single plane angiography. These remain potential limitations of this study.

There are several other factors which potentially could be important in influencing the left ventricular diastolic pressure-volume curve. Methoxamine could act directly on the myocardium to impair left ventricular relaxation. In cat papillary muscles, methoxamine causes a slight prolongation of the time for isometric tension to fall to one-half its peak value (RT 1/2) (Rabinowitz *et al.*, 1975), but studies in man have failed to show any direct effect on myocardial function (Goldberg *et al.*, 1960), and it is unlikely that our observations can be explained by a direct effect of methoxamine on left ventricular relaxation. Methoxamine could also potentially impair left ventricular relaxation by inducing myocardial ischaemia due to increased systemic arterial pressure and increased myocardial oxygen demands. The patients selected for our study did not have coronary artery disease or evidence of myocardial ischaemia so this mechanism is unlikely.

Secondly, methoxamine could alter viscous and inertial forces by changing the rate of left ventricular filling and this could affect the diastolic pressure-volume relation. In experimental dog studies, Noble *et al.* (1969) noted an upward shift of the left ventricular diastolic pressure-dimension curve in early and late diastole with methoxamine, and attributed these changes to altered viscous and inertial forces caused by more rapid ventricular filling in early and late diastole. In our study, the rate of left ventricular filling was increased in early diastole with methoxamine, but changed little in middle and late diastole. Therefore, it appears that altered viscous forces may contribute to the changes in the pressure-volume relation in early diastole in our patients, but they probably cannot account for the changes in middle and late diastole.

There is experimental evidence in dogs that changes in right ventricular loading may alter left ventricular stiffness (Laks *et al.*, 1967; Taylor *et al.*, 1967; Kelly *et al.*, 1971; Bemis *et al.*, 1974). Increases in right ventricular diastolic pressure change the left ventricular diastolic pressure-volume curve such that left ventricular diastolic pressure is higher at a given volume. Presumably this is because of shifts in the interventricular septum so that it limits left ventricular filling (Bemis *et al.*, 1974). In our subjects right ventricular filling pressures increased significantly with methoxamine, and this mechanism could be important in the acute changes in the pressure-volume relation seen in our patients.

Pericardial restriction also could potentially account for the changes in the pressure-volume relation with methoxamine. The pericardium probably offers no restriction to ventricular filling under normal conditions, but it may be capable of exerting a restrictive function when the heart is distended to large volumes (Holt *et al.*, 1960; Holt, 1970). Increases in left ventricular and presumably right ventricular volumes with methoxamine could encroach upon the limited intrapericardial space and cause restriction to left ventricular filling by the relatively non-distensible pericardium (Glantz *et al.*, 1977; Janicki and Weber, 1977; Shirato *et al.*, 1977). We cannot exclude this mechanism, but one might expect partial equalisation of right ventricular and left ventricular filling pressures at end-diastole, which we did not observe.

In summary, an increase in systemic arterial pressure with methoxamine resulted in a substantial upward shift of the left ventricular diastolic pressure-volume curve and an increase in left ventricular mass in each subject. These changes are probably not the result of intrinsic changes in myocardial properties, since methoxamine has little or no direct effect on the human myocardium and since the patients studied had no evidence of myocardial ischaemia. The increase in left ventricular mass suggests that acute increases in systemic arterial pressure may increase left ventricular stiffness by coronary vascular engorgement and an 'erectile effect' on the left ventricular myocardium. The study cannot exclude pericardial restriction and changes in right ventricular loading as contributing factors in acute shifts in the left ventricular diastolic pressure-volume curve.

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Persistence and effects of sinus rhythm after Fontan procedure for tricuspid atresia

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SUMMARY Four patients who had had a Fontan type of procedure for tricuspid atresia 23, 6, 9, and 11 months previously were investigated by ambulatory electrocardiographic recording and simultaneous recording of the jugular venous pressure and echocardiogram of the conduit or pulmonary valve. All had been considerably improved by the operation. In 1 patient episodes of supraventricular tachycardia were recorded but no rhythm disturbance was detected in the other 3. Pulmonary blood flow was shown to be pulsatile and atrial systole is an important factor in this. The conduit valve showed delayed opening and slow closure suggesting that its presence in the pulmonary circuit may be unnecessary.

In 1971 Fontan and Baudet reported 3 patients with tricuspid atresia in whom they redirected the entire systemic venous return to the pulmonary circulation by attaching the superior vena cava to the right pulmonary artery and the right atrium, through an aortic homograft valve, to the pulmonary artery bifurcation and hence the left lung. A homograft pulmonary valve was inserted into the inferior vena cava, the atrial septal defect closed, and the main pulmonary artery ligated.

With more experience of the technique (Ross and Somerville, 1973; Henry *et al.*, 1974; Somerville and Ross, 1975; Stanford *et al.*, 1975; Walker *et al.*, 1975), modifications have been introduced. In some cases the right atrium has been connected to the outlet chamber (Somerville and Ross, 1975) and there is debate regarding the need for caval valves (Fontan *et al.*, 1977; Yacoub, 1977). The technique has also been extended to other forms of the hypoplastic right heart syndrome (Yacoub *et al.*, 1975; Sharratt *et al.*, 1976).

In all variants of the operation atrial systole appears to be necessary for a good result (Ross and Somerville, 1973; F. Fontan, 1977, personal communication). The present study was performed to investigate the role that atrial systole plays in pulmonary blood flow and to see if there are any indications that sinus rhythm may not be maintained after this procedure.

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Subjects and methods

Four patients with tricuspid atresia, who had successfully undergone the Fontan operation, were studied.

Echocardiograms and the externally derived jugular venous pulse wave (JVP) were recorded on a Cambridge strip-chart recorder. Echocardiography was performed using a Smith Klein Ekoline 20 and a 2·25 MHz transducer focused at 5 cm. The transducer position varied according to the site of the conduit or pulmonary valve.

Ambulatory electrocardiographic recordings were made on an Oxford Medilog dynamic cardiogram recorder and these were analysed on a Reynolds Pathfinder electrocardiograph analyser.

CASE 1

This patient was born in 1951. At the age of 6 years a left Blalock-Taussig shunt was performed for increasing dyspnoea and cyanosis. In 1965 he had his first episode of palpitation and these occurred occasionally from then on. The electrocardiogram showed sinus rhythm with a PR interval of 0·09 s (Fig. 1A) suggesting the presence of the Lown-Ganong-Levine syndrome. Periods of high junctional rhythm (coronary sinus rhythm) (Fig. 1B) and a tachycardia of 130/min arising from this same focus (Fig. 1C) were also recorded.

In 1973 repeat cardiac catheterisation disclosed atrial situs solitus, univentricular heart with anterior outlet chamber, discordant arterial connections with

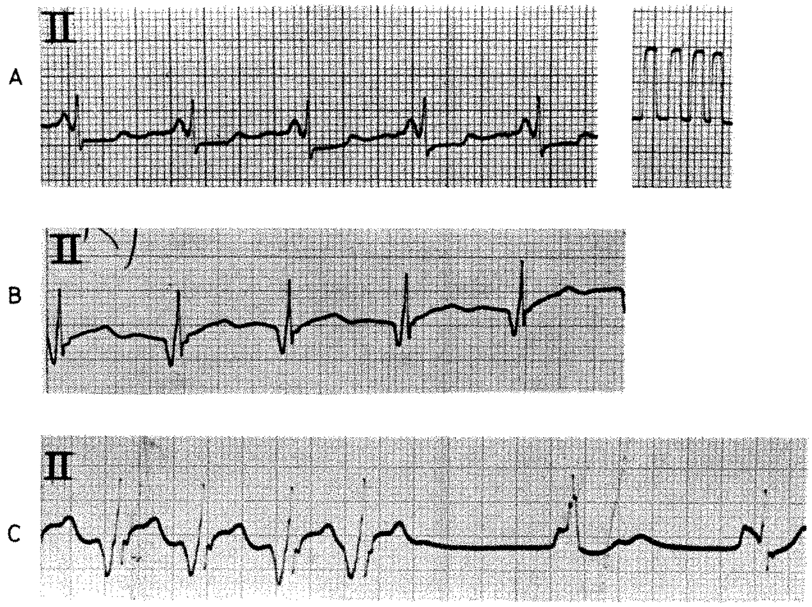

Fig. 1 *Preoperative electrocardiograms in case 1.*

pulmonary outflow tract obstruction, and atresia of the right atrioventricular valve and a secundum atrial septal defect. The Blalock-Taussig shunt was virtually functionless. The pulmonary artery pressure was 12/5 mmHg. On 16 April 1975 a Fontan procedure was performed. The main pulmonary artery was ligated and a size 21 mm homograft valve conduit inserted between the right atrial appendage and the right pulmonary artery. The atrial septal defect was closed by direct suture. No valves were placed in the inferior or superior vena cava.

He was asymptomatic 32 months after the operation and leading a full and active life as an electrical engineer. The jugular venous pulse had an A wave visible to 6 cm above the sternal angle but there was no hepatomegaly or oedema.

CASE 2

This boy was born in 1969. At the age of 10 months a left Blalock-Taussig anastomosis was performed with some improvement. By 1977, however, he had deteriorated to such an extent that he was almost confined to a wheel-chair. The diagnosis was dextrocardia, visceral and atrial situs solitus, and double outlet univentricular heart without a rudimentary chamber; the aorta was anterior and slightly to the right of the pulmonary artery; there was pulmonary outflow tract obstruction, and atresia of the right atrioventricular valve with a secundum atrial septal defect and a non-functioning left Blalock-Taussig anastomosis. At operation on 24 August 1977, the main pulmonary artery was ligated and a size 18 mm antibiotic sterilised homograft valve was inserted between the right atrial appendage and the right pulmonary artery. The atrial septal defect was closed by a pericardial patch and no caval valves were inserted. Six months later he was asymptomatic and beginning to take part in physical education at school. There was a 4 cm A wave in the jugular venous pulse but no hepatomegaly or peripheral oedema.

CASE 3

This girl was born in 1965. In 1967 a right Blalock-Taussig anastomosis was performed. She remained fairly well with moderately reduced effort tolerance. Reinvestigation indicated atrial situs solitus, univentricular heart with an anterior outlet chamber, and normally connected great arteries. There was pulmonary outflow tract obstruction, atresia of the right atrioventricular valve, and a secundum atrial septal defect. The right Blalock-Taussig shunt was not functioning. On 20 April 1977 a Fontan procedure was performed. The main pulmonary artery was ligated and a size 18 mm antibiotic sterilised homograft valve was inserted between the right atrial appendage and the right pulmonary artery. The atrial septal defect was closed with a pericardial patch and the old Blalock-Taussig anastomosis was ligated. No caval valves were inserted. Eleven months later she was asymptomatic and able to take part in physical education at school. She had a 5 cm A wave in the jugular venous pulse but no hepatomegaly or peripheral oedema.

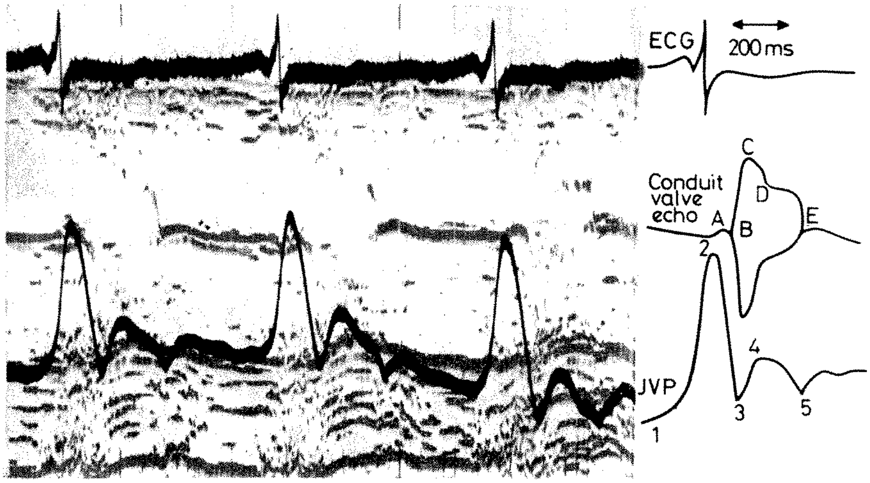

Fig. 2 *Simultaneous electrocardiogram (ECG), conduit valve echo, and jugular venous pulse (JVP) in case 1. See text for description.*

CASE 4

This boy was born in 1963. At the age of 5 years a Waterston shunt was performed, with some improvement, but he became progressively more cyanosed and effort tolerance declined. At repeat cardiac catheterisation in 1973 atrial situs solitus, univentricular heart with anterior outlet chamber, normally connected great vessels with pulmonary outflow tract obstruction, atresia of the right atrioventricular valve, and a secundum atrial septal defect were confirmed. The Waterston anastomosis was still functioning. Pulmonary vascular resistance was 14 per cent of the systemic vascular resistance and the pulmonary artery pressure was 18/4 mmHg. On 29 June 1977 a Fontan procedure was performed. The bulboventricular foramen was closed and a size 18 mm antibiotic sterilised homograft valve was inserted between the right atrial appendage and the outlet chamber. The atrial septum was closed with a pericardial patch and the Waterston shunt was closed. No caval valves were inserted. Recovery was uneventful and 9 months after the operation he was asymptomatic and played football, basket ball, cricket, and golf. There was a 6 cm A wave in the jugular venous pulse with no hepatomegaly or oedema.

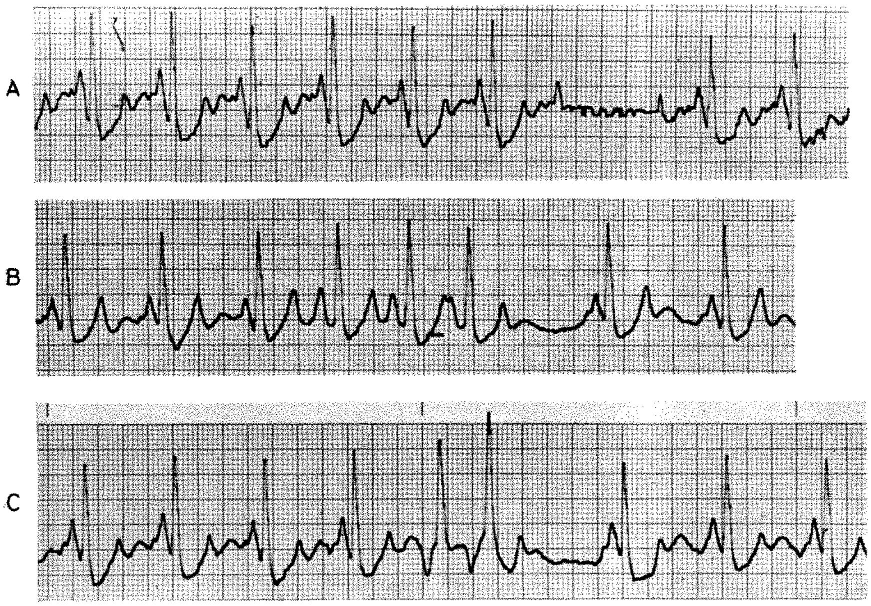

Fig. 3 *Extracts from ambulatory electrocardiogram in case 1.*

Results

CASE 1

Echocardiography (Fig. 2)
Opening of the conduit valve (B) begins 80 ms after the peak of the A wave of the jugular venous pulse waveform (2). It is preceded by a small anterior movement (A). The X descent begins before the valve opens and continues to decline sharply until the valve achieves its maximal opening (C). The cusps then become more closely apposed (D) and there is a small rise in the jugular venous pulse (4). The valve then closes (E) and there is a brief dip in the jugular venous pulse (5). The valve is open for 250 ms.

Ambulant electrocardiogram
The sinus rate varied from 70/min (during sleep) to 125/min. The only conduction disorder recorded is shown in Fig. 3A. Two types of atrial extrasystoles were recorded, one with an upright P wave, and one with an inverted P wave similar to the preoperative abnormal rhythm. Only 4 of the first type were recorded, 1 in isolation and 3 in succession (Fig. 3B). Twelve of the second type were recorded, 5 in isolation, 2 periods in pairs (Fig. 3C) and 1 episode of 3 in succession. Ninety-six ventricular extrasystoles were recorded, all as single beats. The tape time was 24 hours.

CASE 2

Echocardiography (Fig. 4)
The echo of the conduit valve is incomplete but it is seen in its fully open position and during its closing movement, which is more gradual than in case 1. The jugular venous pulse is very similar to that described for case 1.

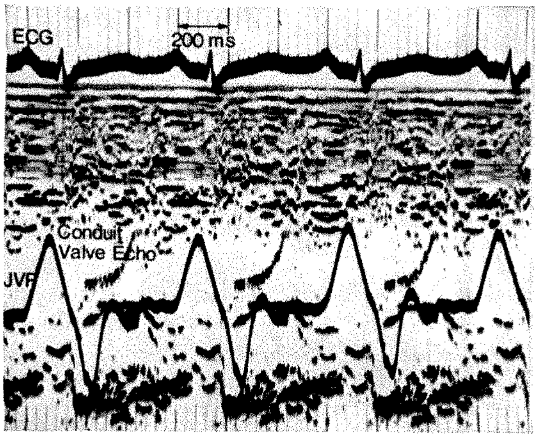

Fig. 4 *Simultaneous electrocardiogram (ECG), conduit valve echo, and jugular venous pulse (JVP) in case 2.*

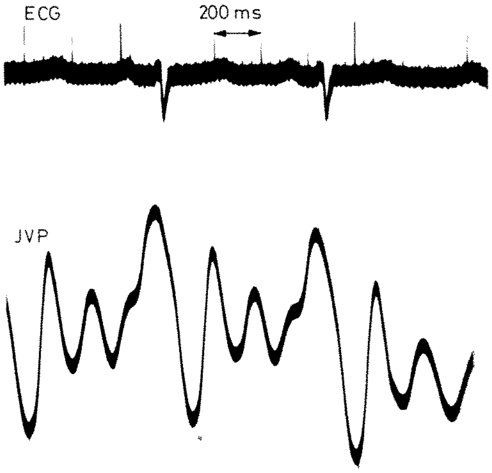

Fig. 5 *Electrocardiogram (ECG) and jugular venous pulse (JVP) in case 3.*

Ambulant electrocardiogram
The heart rate varied from 65/min (during sleep) to 110/min. There were 4 atrial extrasystoles and 1 ventricular extrasystole recorded during the 22-hour recording period.

CASE 3

Echocardiography
It was not possible to record the conduit valve and

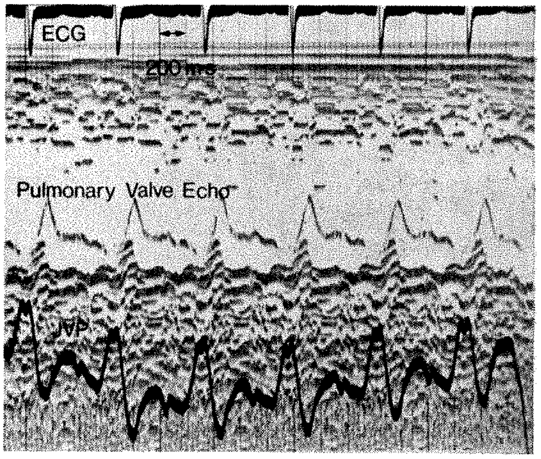

Fig. 6 *Simultaneous electrocardiogram (ECG), pulmonary valve echo, and jugular venous pulse (JVP) in case 4.*

no pulmonary valve was present in the pulmonary circulation. Jugular venous pulse (Fig. 5) was similar to those recorded in the other patients.

Ambulant electrocardiogram
The heart rate varied from 83/min (during sleep) to 150/min. Five ventricular extrasystoles and 3 atrial extrasystoles were recorded. The tape time was 24 hours. Tape analysis was complicated by a large P wave which could not be reduced by changing the electrode position.

CASE 4

Echocardiography
The conduit valve could not be recorded but the patient's own pulmonary valve was recorded. It is seen to follow a similar pattern to that of the conduit valve in case 1 (Fig. 6). Opening begins 40 ms after the peak of the A wave of the jugular venous waveform, the valve starts to open and its point of maximum opening coincides with the nadir of the dip in the venous wave. There is then partial closure of the cusp. The point of final closure is not accurately defined.

Ambulant electrocardiogram
The heart rate in sinus rhythm varied between 72/min (during sleep) and 150/min. Eleven isolated atrial extrasystoles were recorded (Fig. 7A), a 20-second burst of atrial tachycardia with a rate of 146/min (Fig. 7B) and a 30-second burst with a rate of 200/min (Fig. 7C). The first episode was asymptomatic while during the second episode the patient experienced severe cramp in a leg though it is not clear whether this was the initiating event or occurred during the paroxysm. The tape time was 22 hours.

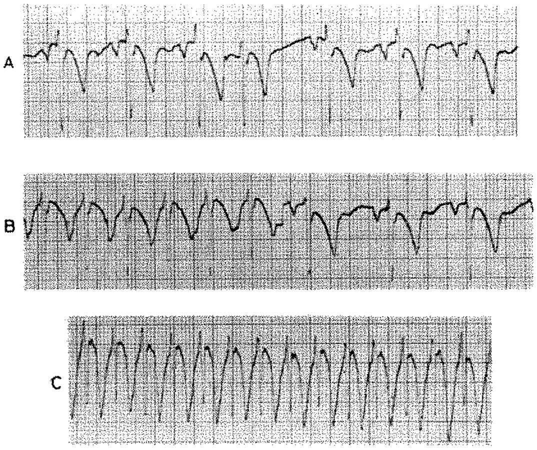

Fig. 7 *Extracts from ambulatory electrocardiogram in case 4.*

Discussion

Severe vascular changes may occur in the right lung after a superior vena cava pulmonary artery anastomosis (Achtel *et al.*, 1969; McFaul *et al.*, 1976). This appears to be related to sluggish blood flow (Laks *et al.*, 1977). It, therefore, seems important after the Fontan procedure for tricuspid atresia that atrial systole is maintained if it is true that atrial systole contributes significantly to the rate of pulmonary blood flow. This certainly appears to be the case as the loss of atrial systole, for example when atrial fibrillation occurs, results in systemic congestion which resolves after the restoration of sinus rhythm by DC cardioversion (F. Fontan, 1977, personal communication). The present investigation was undertaken in an attempt to delineate the contribution of atrial systole to pulmonary blood flow and to assess the likelihood that sinus rhythm might not be maintained in the 4 patients studied.

Echocardiograms of the conduit valve in cases 1 and 2 and of the pulmonary valve in case 4 certainly showed that pulmonary blood flow was pulsatile and that atrial systole was an important factor in this. The jugular venous waveform appeared to have a very similar pattern in all 4 patients. We believe that the sequence of events, shown in Fig. 2, is right atrial isovolumic contraction (point 1 to point B) which moves the closed valve slightly forward (point A). The valve appears to have some inertia which has to be overcome, the jugular venous pulse declining before the valve opens. With opening of the valve there is a sharp fall in the venous waveform, maximal (point 3) at the point of widest opening of the valve (point C). The subsequent rise in the venous pulse (point 4) is probably the result of venous return, entering the atrium with atrial relaxation. At this point the valve is still open but less widely so (point D). There follows a slow fall in the venous pulse then to point 5 at which time the valve closes (point E) and the venous pulse then rises again presumably because of atrial filling with the conduit valve closed. The right atrial ejection time in case 1, as measured from point B to point E, is about 250 ms. The normal left ventricular ejection time that one would expect at that heart rate would be about 280 ms (Weissler *et al.*, 1961). The right atrium is therefore acting as an efficient pump.

In case 4 the conduit was attached to the ventricular outlet chamber. The pulmonary valve echo would therefore be expected to show the effects of outlet chamber systole. However the movement of the pulmonary valve (Fig. 7) is similar to that of the conduit valve in the other patients, and there is no additional opening movement that could be attributed to contraction of the outlet chamber. The outlet chamber was known to be small.

It is difficult to reach firm conclusions from the results of the ambulant electrocardiographic monitoring because of the lack of control data. The minimum sinus rates of cases 1, 2, 3, and 4 were 70, 65, 83, and 72 beats per minute, respectively. These are high when compared with the normal population studied by Brodsky *et al.* (1977). There the minimum sinus rates were between 37 and 65 beats per minute but the population was older at 23 to 27 years. In cases 2 and 4 no untoward events were recorded. The atrial tachycardia in case 4 must raise a question as to the long-term outlook for the maintenance of atrial systole in him. Case 1, despite the preoperative occurrence of atrial tachyarrhythmias, had only 1 burst of 3 atrial extrasystoles in a row but he did have 96 ventricular extrasystoles over the 24-hour period, which is probably excessive (Brodsky *et al.*, 1977). It is of interest that he was the oldest patient operated on and dysfunction of the primitive ventricle may occur if it has to handle a large volume for a long time (F. Fontan, 1977, personal communication). This may be relevant to the occurrence of the extrasystoles in this patient.

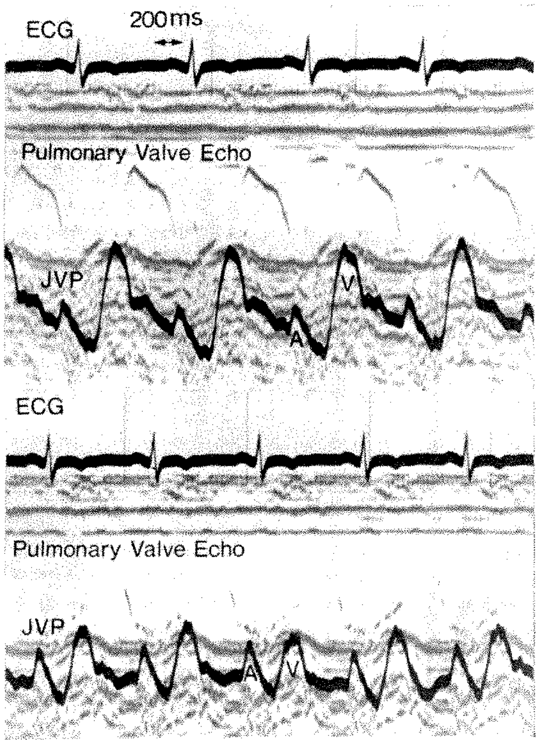

Fig. 8 *Simultaneous electrocardiogram (ECG), jugular venous pulse (JVP), and echocardiogram of the pulmonary valve in the presence of valved conduit attached to a large outlet chamber. The top tracing shows the opening movement of the pulmonary valve; the bottom tracing shows the valve in its open position.*

There is no doubt that there has been dramatic symptomatic improvement in these patients in the short time that they have been followed (23, 6, 9, and 11 months) and there is not the hazard of a right-to-left intracardiac shunt which remains in other forms of palliation for tricuspid atresia.

Our results encourage us to continue using this procedure though the arrhythmias in case 4 give cause for concern. It is our impression that caval valves do not improve the haemodynamics and indeed in view of the apparent opening inertia of the conduit valve it could be questioned whether any valves are required at all. When the outlet chamber is used, we believe that a valve should be inserted between the right atrial appendage and the outlet chamber. This conclusion is based upon our experience with 2 patients, not fully reported here. In one of these patients a 'dacron' tube was used and the patient died after 2 years, with systemic venous congestion. At necropsy, however, a fenestrated mitral valve cusp was found and this must have produced significant mitral regurgitation. In the second patient, recently operated upon, a valved conduit was used between the right atrial appendage and a large outlet chamber. The postoperative course was uneventful and the echocardiogram of the pulmonary valve (Fig. 8) shows no opening inertia, the rapid opening movement coinciding with the onset of the upstroke of the A wave of the jugular venous pulse, and the valve remains fully open during what appears to be an X descent and V wave. The valve closes at the peak of the V wave. There is thus, in this patient, clear evidence of outlet chamber systole. However case 4 in this series indicates that a small outlet chamber, after it has been opened and a conduit inserted, has little or no mechanical activity.

We thank Mr M. Sturridge for permission to study case 1 on whom he performed the operation.

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Prinzmetal's angina: reflex cardiovascular response during episode of pain

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SUMMARY Previous angiographic studies have shown that coronary spasm occurs in association with the variant angina described by Prinzmetal, confirming his original hypothesis. In this work we recorded the heart rate changes and the incidence of arrhythmias during variant angina. The patients were divided into two groups: anterior, with electrocardiographic signs of anterior ischaemia, and inferior, with changes in the inferior leads. There was a significant increase of heart rate during pain in anterior myocardial ischaemia and a significant decrease when the ischaemia was inferior. The incidence of ectopic arrhythmias during pain was significantly greater in patients with anterior ischaemia, but there was a high incidence of atrioventricular block in patients with inferior ischaemia. We suggest that these findings can be explained by different responses of the autonomic nervous system to anterior and inferior acute myocardial ischaemia.

The angina described by Prinzmetal *et al.* in 1960 is a clinical entity which can be differentiated from classic angina pectoris: (a) *Clinically:* classic angina is regularly preceded by an increase in cardiac work, resulting from an increase in heart rate, peripheral resistances, or ventricular pre-ejection time (Roughgarden, 1966; Robinson, 1967). On the other hand, Prinzmetal angina can appear at rest and is not preceded by changes in these variables (Guazzi *et al.*, 1971b). (b) *Electrocardiographically:* the electrocardiogram during classic angina pectoris is characterised by depression of the ST segment and/or T wave inversion. Prinzmetal angina is accompanied by transient ST segment elevation which returns to normal once the pain has passed off. (c) *Coronary arteriography:* various investigators, the first of whom were Dhurandhar *et al.* (1972) and Oliva *et al.* (1973), have confirmed Prinzmetal's theory that coronary spasm occurred during the episode of variant angina but not during classic angina. This observation shows the similarity between the patients with Prinzmetal's angina and experimental animals subjected to transient coronary ligature. This group of patients are, therefore, ideal for the study of the circulatory changes produced by acute myocardial ischaemia.

In previous studies during coronary arteriography (Perez-Gomez and Garcia-Aguado, 1977), we found a dominant response of the parasympathetic receptors situated in the inferior wall of the left ventricle. In this investigation we have studied changes in heart rate and rhythm during episodes of pain in patients with Prinzmetal's angina.

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Subjects and methods

We made observations on 14 patients with the clinical diagnosis of Prinzmetal's angina who were divided into 2 groups. *Group A* consisted of 7 patients with the typical electrocardiographic changes of Prinzmetal's angina in the anterior praecordial leads, and *group I* consisted of 7 patients with these changes in left ventricular inferior wall leads. Coronary arteriography was performed on 12 patients and left ventriculography on 10. The changes in heart rate produced by the pain were recorded in 12 patients.

In order to obtain a large number of patients for statistical purposes, we have reviewed the electrocardiographic tracings in 63 published cases where both the basal electrocardiogram and the electrocardiogram during pain were shown. These cases are those described by Prinzmetal *et al.* (1960), cases 1 and 2; Robinson (1965); Botti (1966); Schwartz *et al.* (1966), case 1; Hilal and Massumi (1967); Dorra *et al.* (1968); Jouve *et al.* (1969), cases 2, 4, 6, 7, and 8; Poggi *et al.* (1969), 2 cases; Whiting *et al.* (1970); Bayes de Luna *et al.* (1971), 2 cases; Casamayor del Cacho *et al.* (1971); Guazzi *et al.* (1971a), cases 1,3,4, and 5; Silverman and Flamm

(1971), case 1; Cosby *et al.* (1972), cases 1 and 3; Cheng *et al.* (1973), cases 1, 2, 3, and 4; Cherrier *et al.* (1973), case 7; Ferrer Montagut *et al.* (1973), case 2; MacAlpin *et al.* (1973), cases R.C., C.G., and M.K.; MacMillan *et al.* (1973), case R.W.; Oliva *et al.* (1973); Bodenheimer *et al.* (1974), cases 2, 6, and 7; Gaasch *et al.* (1974), case 3; Kossowsky *et al.* (1974), case 4; Levin *et al.* (1974), 3 cases; Schroeder *et al.* (1974); Vázquez Garcia *et al.* (1974), case 6; Yasue *et al.* (1974), cases M.S., S.S., and H.K.; Donsky *et al.* (1975); Endo *et al.* (1975), cases 2 and 9; Gaasch *et al.* (1975), cases 1 and 2; Smithen *et al.* (1975); Widlansky *et al.* (1975); Marsh *et al.* (1976); Daniel Riesco *et al.* (1976), cases 1 and 2; and Yasue *et al.* (1976), cases 1, 2, 3, and 4. With our 12 cases, there is a total of 75 published cases, of which 38 belong to group A, and 37 to group I. We have excluded those patients who presented with myocardial infarction or severe coronary artery disease in an area other than that which gave rise to the electrocardiographic abnormalities. We also excluded those patients in whom electrocardiograms showed atrioventricular block and those in whom sinus rhythm and ventricular arrhythmias alternated, unless sufficient of the record showed normal sinus rhythm. We compared the basal rate with the rate during pain, measuring average heart rate from all the tracings shown in the publication.

We studied the incidence of arrhythmias during pain in 210 cases, including our 14 cases, cases reported by the authors listed above, and cases reported by Meriel *et al.* (1966), Bouvrain *et al.* (1969), Gillilan *et al.* (1969), Hardel *et al.* (1969), Yeh and Rogers (1970), Gaquière and Quillet (1971), Guazzi *et al.* (1971b), Cheng *et al.* (1972), Dhurandhar *et al.* (1972), Kemp (1972), Fernandez *et al.* (1973), Gonin *et al.* (1973), Hiltgen *et al.* (1973), King *et al.* (1973), Levi and Proto (1973), Applefield and Ronan (1974), Auzépy *et al.* (1974), Betriu *et al.* (1974), Hart *et al.* (1974), Kerin and Macleod (1974), Kerin and Schwartz (1974), Nevins (1974), Prchkov *et al.* (1974), Harper *et al.* (1975), Marti Garcia *et al.* (1975), Meller *et al.* (1975), and Shubrooks *et al.* (1975). Cases were included only if the area of ischaemia and the occurrence or absence of arrhythmias was specifically stated.

Applying the same criteria we divided the cases into two groups: group A (anterior) with 104 cases, group I (inferior) with 101 cases, and group I+L (inferior and lateral) with 5 cases. The incidence of ectopic arrhythmias and of second or third degree atrioventricular block was analysed. In each case we only considered the most severe arrhythmia (classifying severity in the following order: ventricular fibrillation, ventricular tachycardia, ventricular ectopic beats, atrial fibrillation, atrial tachycardia, and atrial ectopic beats). However, we have taken into account the association of atrioventricular block and severe ventricular arrhythmias (ventricular fibrillation or tachycardia).

Results

LEFT VENTRICULAR HAEMODYNAMICS (Table 1)
Basal left ventricular end-diastolic pressure was normal in all cases, ranging from 5 to 12 mmHg. The ejection fraction was greater than 0·5 in all cases, except for one in which it was 0·41.

CORONARY ARTERIOGRAPHY (Table 1)
Obstruction greater than 50 per cent was found in 9 patients, involving 1 artery in 7, and 2 arteries in the remaining 2. The coronary arteries were normal in 2 patients and were slightly abnormal in another.

Table 1 *Clinical, haemodynamic, and angiographic data*

Case no.	*Age*	*Sex*	*Sinus rate*		*Area of ST ↑*	*Arrhythmias*	*LVEDP*	*Ejection fraction*	*Coronary arteriography*			
			Basal	*Pain*					*AD*	*AD (branches)*	*Cx*	*RC*
1	44	M	115	95	I	—	12	0·66	—	—	25	75(x)
2	45	M	85	57	I	—	8	0·72	—	—	25(x)	—
3	51	M	95	62	I	—	—	—	30	—	—	100
4	46	M	60	130	A	VE	10	0·77	75	—	—	25
5	50	M	72	90	A	—	—	—	—	—	—	—
6	65	M	78	100	A	AF	—	—	—	—	—	—
7	41	F	65	85	A	VE	8	0·41	75	—	—	50
8	56	M	—	—	—	—	10	0·55	—	75	50	—
9	51	M	60	45	I	AV block	—	0·85	—	50	—	—
10	44	M	68	98	A	—	6	0·74	50	—	—	—
11	44	M	75	63	I	—	10	0·71	50	—	—	25(x)
12	51	M	60	—	I	—	5	0·76	—	—	—	90
13	58	M	62	75	A	—	12	0·74	—	—	—	90
14	68	M	115	95	I	—	—	—	—	—	—	100(x)

I, inferior ischaemia; A, anterior ischaemia; VE, ventricular ectopics; AF, atrial fibrillation; LVEDP, left ventricular end-diastolic pressure; AD, anterior descending; Cx, circumflex; RC, right coronary.
Data of coronary arteriography expressed in percentage of obstruction. (x), obstruction caused by spasm.

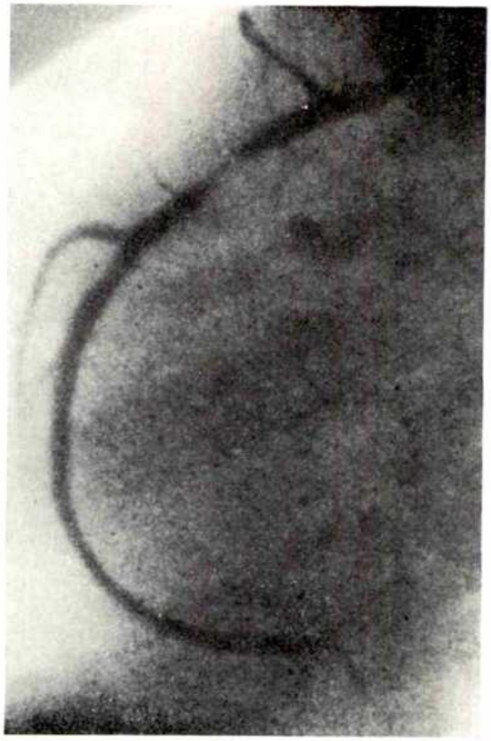

Fig. 1 *Right coronary arteriogram in left anterior oblique projection showing severe obstruction.*

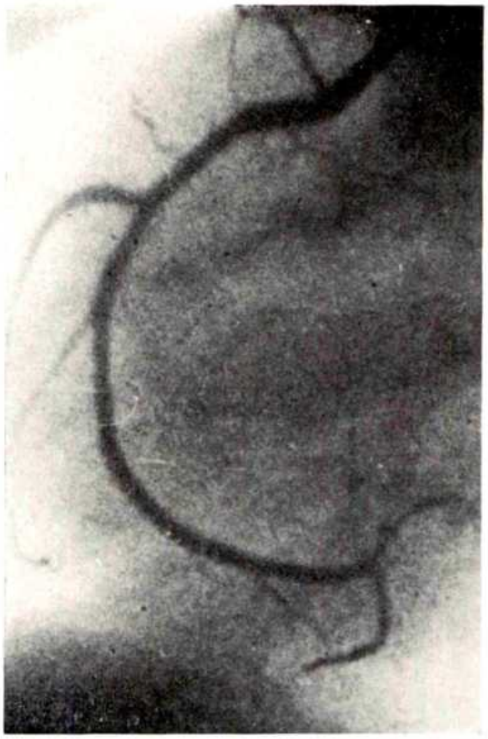

Fig. 2 *Same case as in Fig. 1, after administration of glyceryl trinitrate, showing normal coronary artery.*

Distal arteries were normal in all cases. Arteriography showed coronary spasm in 4 cases (Fig. 1 and 2), appearing spontaneously in 3 and after adrenaline injection in the other. In 1 patient the spasm affected the entire length of the anterior descending artery, the contrast medium taking several seconds to reach the peripheral branches. In all cases the spasm passed off after the administration of sublingual glyceryl trinitrate.

CHANGES IN HEART RATE DURING EPISODE OF PAIN

Group A

Mean sinus rate increased with pain from a basal rate of 67·5 beats per minute to 94·6, a change which was statistically significant (Fig. 3). In all published cases, the mean basal rate was 69·3 increasing during pain to 86·3, a highly significant change (Fig. 4).

Group I

The mean basal rate in our cases was 90·9 beats per minute which decreased during pain to 69·5, a change which was not statistically significant (Fig. 3). In all published cases, the mean basal rate was 76·5

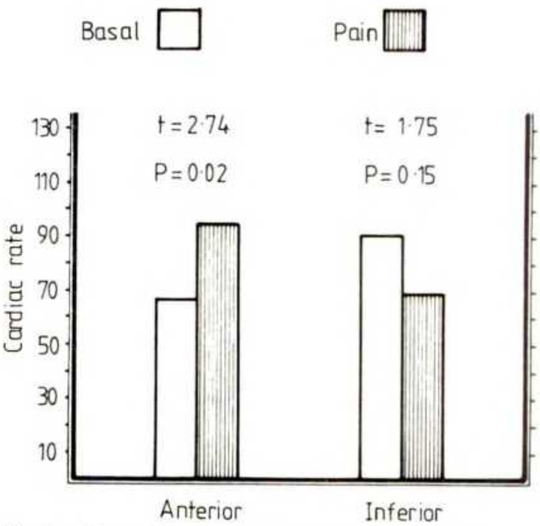

Fig. 3 *Change in heart rate during pain in our cases. There is an increase of rate in patients with anterior ischaemia and decrease in those with inferior ischaemia.*

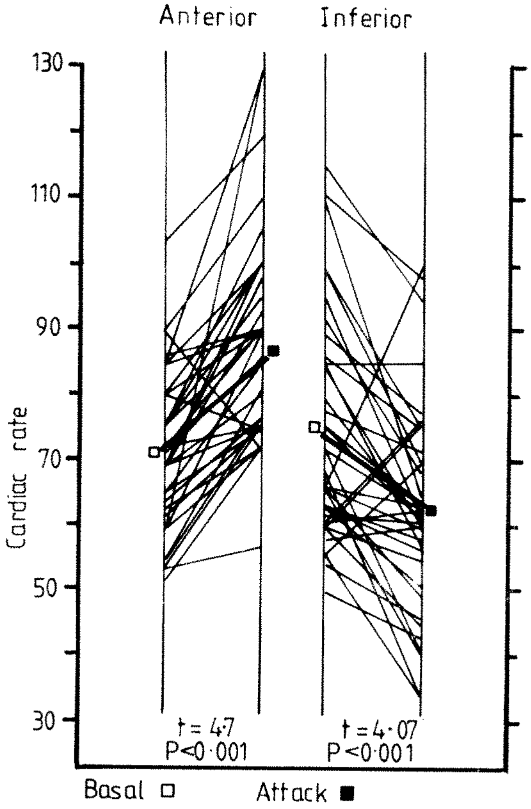

Fig. 4 *Change in heart rate during pain in all published cases.*

which fell during pain to 64·6, a highly significant change (Fig. 4).

ARRHYTHMIAS DURING EPISODE OF PAIN

Group A

One of our patients developed atrial fibrillation and 2 ventricular ectopic beats. Of the 104 published cases (Table 2), 30 developed severe ventricular arrhythmias (tachycardia or fibrillation) during pain, 22 had ventricular ectopic beats, and 5 had atrial arrhythmias. Three cases (Table 3) had atrioventricular block, which in 2 was accompanied by a severe ventricular arrhythmia. One of these cases had had previous inferior myocardial infarction, one other had severe right coronary artery disease, and the other slight narrowing of the anterior descending coronary artery.

Group I

One of our cases developed atrioventricular block but none developed ectopic arrhythmias. Of the 101 published cases, however, 4 had severe ventricular arrhythmias, and 6 ventricular ectopic beats. Severe ventricular arrhythmias associated with atrioventricular block were reported in 8 cases (Table 3) and isolated atrioventricular block in 17. Statistical analysis showed that ectopic arrhythmias occurred more commonly in group A than in group I, both when these arrhythmias were seen in isolation (P < 0·001), and when those associated with atrioventricular block were included (P < 0·005).

Discussion

Coronary arteriography during the episode of Prinzmetal's angina, first performed by Dhurandhar *et al.* (1972) and Oliva *et al.* (1973), and subsequently by others, has confirmed the occurrence of the transient coronary spasm which was postulated by Prinzmetal *et al.* (1960) as the cause of this syndrome. Recent studies have shown that coronary spasm accompanied by the classical symptoms can be reproduced by the injection of methacholine (Yasue *et al.*, 1974), ergometrine (Gaasch *et al.*, 1975), or adrenaline in the presence of beta-adrenergic blockade (Yasue *et al.*, 1976). For this reason, the patient with Prinzmetal's angina is an ideal subject for the study of the circulatory and central nervous system reponses to transient acute myocardial ischaemia. During the episode of pain the characteristic haemodynamic change is a conspicuous rise in left ventricular end-diastolic pressure reflecting left ventricular dysfunction. In the cases published by Guazzi *et al.* (1971b), Cheng *et al.* (1973), Kerin and Macleod (1974), Levin *et al.* (1974), Gaasch *et al.* (1975), and Smithen *et al.* (1975), there was no difference in haemodynamic behaviour between patients with anterior and those with inferior ischaemia. We believe, therefore, that the dependence of heart rate response on the site of coronary spasm

Table 2 *Arrhythmias during pain*

	Ventricular tachycardia	*Ventricular fibrillation*	*Ventricular ectopic beats*	*Atrial fibrillation*	*Atrial ectopic beats*	*Supraventricular tachycardia*
Anterior	16	14	22	1	1	3
Inferior	3	1	6	1	–	–
Inferior + lateral	–	1	1	–	–	–

Table 3 *Atrioventricular block during pain*

	Isolated AV block	*Atrioventricular block*	
		+ Ventricular tachycardia	*+ Ventricular fibrillation*
Anterior	1	1	1
Inferior	17	6	2
Inferior + lateral	–	–	2

implies a difference in the response of the autonomic nervous system to anterior and inferior ischaemia, with a predominant sympathetic response to anterior ischaemia, and a predominant parasympathetic response to inferior ischaemia. This difference has not been recognised in the past because there have been few published cases and because they have not been divided into those with anterior and those with inferior ischaemia.

The appearance of ectopic arrhythmias is facilitated by a slow heart rate, because of the longer non-refractory diastolic period. Whiting *et al.* (1970) have shown that severe ventricular arrhythmias accompaning atrioventricular block ceased after the implantation of a demand pacemaker, even when episodes of pain continued. However, we have found that the incidence of ectopic arrhythmias is greater in the patients with a faster sinus rate (that is, those with anterior ischaemia). This may result from sympathetic stimulation, as suggested by Daggett and Wallace (1966), increased myocardial oxygen consumption resulting from tachycardia, or the greater extent of myocardial damage which follows the obstruction of the anterior descending artery. Nevertheless, this greater damage can be partly caused by increased heart work because of tachycardia and a high degree of catecholamine release.

There are cases which cannot be included in either of the two principal groups, in whom ST elevation occurs during pain in I, aVL, V5 to V6, *and* inferior leads; Wiener *et al.* (1976) have shown simultaneous spasm of the three main coronary arteries in one of these cases.

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Transmembrane potential changes and ventricular fibrillation during repetitive myocardial ischaemia in the dog[1]

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SUMMARY Electrophysiological changes occurring soon after experimental coronary occlusion have been examined in 13 dogs by combined recording of epicardial action potential, endocardial-epicardial conduction time, and epicardial ST segment elevation during successive 5-minute occlusions of the left anterior descending coronary artery. After initial coronary occlusion, action potential duration shortened from 182 ± 9 ms to 113 ± 9 ms at 2 minutes and conduction time was prolonged from 24 ± 1 ms to 71 ± 17 ms associated with progressive ST segment elevation. These changes were followed by the appearance of potentials of 'slow response' type morphology, alternans of action potential duration and amplitude, alternans of epicardial and endocardial ST segment elevation, and intermittent conduction block. Ventricular fibrillation was preceded by action potential alternans in 95 per cent and by conduction block in 65 per cent of instances and occurred at a time of maximum conduction delay. These data strongly support the concept of re-entry in the pathogenesis of early ventricular fibrillation.

Changes in action potential duration and conduction time were significantly greater during the first occlusion compared with subsequent occlusion periods. There was no significant difference however between data taken from occlusions 2, 3, 4, or 5. This questions the validity of experimental studies of myocardial ischaemia based on comparisons of sequential coronary occlusions using the first as the control.

The high incidence of arrhythmias and sudden death occurring in the first 2 hours of ischaemia in man can be related to the early phase of malignant ventricular arrhythmias that occurs soon after coronary occlusion in experimental animals (Harris, 1950; Oliver, 1976). Understanding of the pathogenesis of such arrhythmias in experimental animals has been largely derived from *in vitro* measurement of electrophysiological variables (Cranefield *et al.*, 1972; Wit *et al.*, 1974) or from intracellular recordings in the isolated perfused heart (Kardesch *et al.*, 1958; Downar *et al.*, 1977b). Pronounced slowing of conduction and heterogeneity of refractoriness have been shown in the ischaemic myocardium consistent with the initiation of arrhythmias by re-entrant excitation (Han, 1969; Cox *et al.*, 1973; Scherlag *et al.*, 1974; Russell and Oliver, 1978).

Little is known however of the relation between transmembrane potential changes and arrhythmias in acute ischaemia. Assessment of this relation is most relevant when examined in the in situ heart and is possible by using the floating microelectrode technique (Woodbury and Brady, 1956; Prinzmetal *et al.*, 1962; Czarnecka *et al.*, 1973). We have recently described a technique for combined intracellular and extracellular recordings of action potential in vivo during acute myocardial ischaemia suited to the assessment of arrhythmogenesis (Russell *et al.*, 1977), and using this combined technique, we report in the present study (a) the relations between intracellular potential changes, endo-epicardial ST segment elevation, and the onset of ventricular fibrillation after coronary artery occlusion, and (b) the reproducibility of these measurements after successive brief coronary artery occlusions in the anaesthetised dog.

Methods

Thirteen mongrel dogs (weight 11 to 15 kg) were

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anaesthetised with sodium pentobarbitone (30 mg/kg intravenously followed by a maintenance infusion of 3 mg/kg per h controlled by a Harvard infusion pump; additional supplements of 3 mg/kg were occasionally required). Sodium chloride 0·9 per cent was infused at 50 ml/h throughout the experiment through a jugular or femoral vein. After intubation with a cuffed endotracheal tube and controlled ventilation with room air, a lateral thoracotomy was performed through the fifth left intercostal space. The heart was suspended in a pericardial cradle and the left anterior descending coronary artery was dissected free 2 to 3 cm from its origin and above its major diagonal branches. Arterial pressure was measured through a femoral arterial cannula using a Statham P23Db strain gauge transducer and displayed on a Devices chart recorder.

Bipolar pacing electrodes were sutured to the left atrial appendage and the heart was paced at 175 beats/min. In 5 dogs, atrial pacing was combined with right vagal stimulation (5 to 10 mA constant current pulse of 4 ms duration at 25 Hz).

Epicardial electrograms were recorded from 5 small disc electrodes (diameter 5 mm) sutured with fine silk to the epicardium within the potentially ischaemic zone of myocardium served by the exposed coronary artery; the electrodes were placed at least 1 cm distant from the probable border of the potentially ischaemic zone and recordings were only obtained after loss of injury potential. A mean signal was derived from an electronic averaging box which also allowed monitoring of any individual lead if required. The endocardial electrogram was recorded within the centre of the potentially ischaemic zone with a plunge electrode of fine insulated copper wire (diameter 0·11 mm) approximately subjacent to the site of epicardial intracellular potential recording.

The cardiac action potential was recorded using our previously reported modification of the floating electrode technique (Russell *et al.*, 1977). Optimal recordings are obtained with thick-wall glass electrodes (2·5 mm external diameter; 1 mm internal diameter) rather than conventional electrodes (1 or 2 mm external diameter). The electrodes were pulled vertically with a slow early phase and a rapid late phase, and then filled with 3M KCl by boiling under reduced atmospheric pressure. Prepared in this way, an acceptable electrode with a short distal tip and an electrical resistance of 10-15 MΩ was obtained. Two floating electrodes were suspended from micro-manipulators and positioned within 1 mm of each other in the centre of the potentially ischaemic area of myocardium. One electrode was impaled to secure an intracellular record, and the other was used as an extracellular indifferent electrode. In some experiments the tip of a fine insulated silver wire was used as the indifferent electrode. The cardiac action potential was recorded by amplifying the potential difference between the electrodes with a high-input impedance amplifier and displaying the output on a DM 63 Tektronic storage oscilloscope using indirect calibration. The signals together with the endocardial and epicardial electrograms were recorded on magnetic tape for subsequent analysis. Selected periods were recorded on paper at 100 mm/s. Sequential measurements of action potential duration (95% repolarisation) were performed. Small variations in diastolic potential which might affect action potential duration determination were eliminated by time measurement from 95 per cent depolarisation to 95 per cent repolarisation. Endocardial-epicardial conduction time, defined as the time from onset of the R wave on the endocardial electrogram to the onset of epicardial activation on the intracellular recording, was also recorded sequentially. Epicardial activation was taken to be at the onset of phase O of the action potential. Small 'extrinsic' potentials resulting from conduction delay between intra- and extracellular electrodes and creating a small foot at the base of phase O were minimised by closer positioning of the reference electrode to the recording electrode and excluded from analysis. Closely reproducible data were obtained from multiple impalements at one site and from continuously recorded control measurements from one electrode before ischaemia. Absolute measurements of transmembrane potential and initial upstroke velocity were not considered valid on account of unavoidable signal distortion caused by movement artefact and variations in microelectrode tip potential. Satisfactory recordings could be maintained over the 5-minute period of occlusion. Data were disregarded after microelectrode tip breakage. Changes in mean epicardial ST segment elevation were derived by continuous computer analysis of the recorded extracellular electrograms (Luxton *et al.*, 1977).

Procedure

In 8 dogs, successive 5-minute occlusions of the coronary artery were achieved with a light spring releasable clip. A 30-minute period of recovery was allowed after each period of ischaemia. When ventricular fibrillation occurred, the occlusive clip was immediately removed and the heart defibrillated by DC countershock (20 watt-second). In no case was correction of acid-base balance required.

Recordings were made before and at 0·5-minute intervals after coronary occlusion of mean epicardial ST segment elevation, endocardial-epicardial conduction time, and cardiac action potential duration at 95 per cent repolarisation.

The effect of variations in heart rate was studied in a further 5 dogs again with a series of 5-minute coronary artery occlusions and 30-minute recovery periods. The first occlusion was undertaken at the dogs' intrinsic heart rate and served to condition the heart to the possible deleterious effects of ischaemia and reperfusion (see Discussion). The second occlusion was undertaken at a heart rate of 100 beats/minute achieved by combined vagal slowing and atrial pacing. During the third and subsequent occlusions, vagal stimulation was continued at the same rate, but the heart rate was increased in increments of 20 beats/minute to a maximum of 200 beats/minute for the seventh and final occlusion.

STATISTICS

All results are expressed as mean ± standard error of mean unless stated otherwise. The significance of difference was tested by Student's t test, paired or unpaired as appropriate.

Results

Before coronary artery occlusion, and with a heart rate of 175 beats/min maintained by atrial pacing, the mean action potential duration was 182 ± 9 ms in 8 dogs. Endocardial-epicardial conduction time was 24 ± 1 ms.

INITIAL CORONARY ARTERY OCCLUSION

Acute coronary artery occlusion was rapidly followed by changes in both the duration and shape of the action potential and increased endocardial-epicardial conduction time.

A representative example is shown in Fig. 1. Rapid action potential shortening was associated with an increase in endocardial-epicardial conduction time within 3 minutes of ischaemia. Potentials then assumed the appearance of 'slow response' potentials (Cranefield *et al.*, 1972), with loss of the initial rapid upstroke phase. Electrical alternans of both action potential and ST segment elevation was evident by 3½ minutes of ischaemia, and 2:1 conduction block was recorded intracellularly after 4 minutes of ischaemia (Fig. 1). In some occlusions more irregular patterns of conduction block occurred.

Mean values over the period of the initial occlusion in 8 dogs are shown in Fig. 2. Mean action potential duration shortened to 140 ± 15 ms at 1 minute ($P < 0{\cdot}001$) and 113 ± 9 ms at 2 minutes ($P < 0{\cdot}001$) though transient prolongation of mean action potential duration was seen in 1 dog within 30 seconds. Loss of action potential amplitude and initial upstroke velocity was observed but not quantified (see Methods). The appearance of 'slow response' wave forms occurred earlier in animals where mean action potential duration shortening was rapid. The progressive shortening of mean

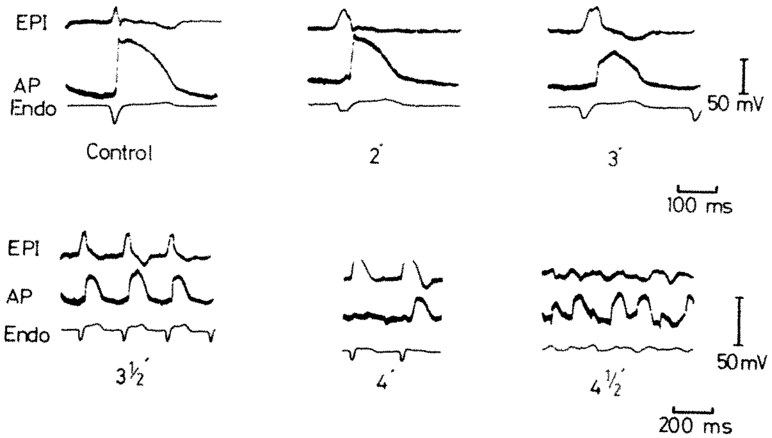

Fig. 1 *Recordings of action potential (AP), endocardial (ENDO), and averaged epicardial (EPI) electrograms from dog heart in situ before and 2, 3, 3½, 4, and 4½ minutes after a coronary artery occlusion. Note shortening of AP at 2 minutes and progressive delay in its onset with respect to the endocardial potential. Electrical alternans occurs at 3½ minutes and localised 2:1 conduction block at 4 minutes recorded from intracellular but not extracellular electrodes. Ventricular fibrillation occurred at 4½ minutes.*

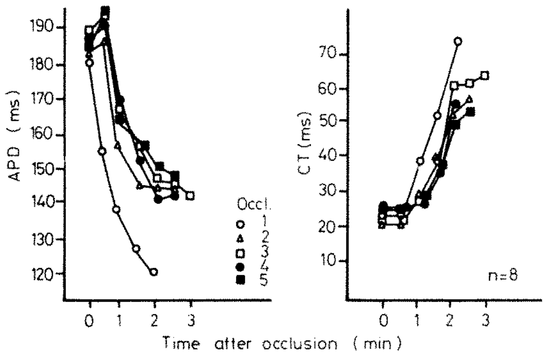

Fig. 2 *Effect of successive 5-minute coronary occlusions on action potential duration and conduction delay in 8 dogs. Note the more pronounced effect of the first occlusion compared with subsequent occlusions. Mean values are shown but data discontinued on initiation of VF in any dog.*

action potential duration was associated in every case with prolongation of endocardial-epicardial conduction time mean values, being 38 ± 5 ms at 1 minute and 71 ± 17 ms at 2 minutes ($P < 0{\cdot}05$). These data are illustrated in Fig. 2 and listed in Table 1.

Interpretation of epicardial ST segment change was made difficult by the appearance of widened epicardial QRS complexes in 5 dogs with severe lengthening of conduction time. However, in 3 dogs, where lesser degrees of conduction time were not associated with QRS widening, mean ST increased to 3·5, 5·3, 7·7, and 11·1 mV at 1, 2, 3, and 4 minutes, respectively, after coronary artery occlusion.

SUCCESSIVE CORONARY ARTERY OCCLUSIONS

After the second coronary artery occlusion, mean action potential duration shortened and endocardial-epicardial conduction time lengthened but at a slower rate than after the first occlusion. Thus, mean action potential duration shortened from 185 ± 9 ms to 157 ± 12 ms at 1 minute, a length significantly greater than that at 1 minute after occlusion 1 ($P < 0{\cdot}005$). Progressive prolongation of endocardial-epicardial conduction time was also more gradual than after occlusion 1 (Table 2). There was, however, no significant difference in the rate of changes in mean action potential duration and conduction time between occlusions 2, 3, 4, and 5 (Fig. 2 and Table 2). Control mean action potential duration showed slight successive prolongation before successive occlusions despite constant heart rate (Fig. 2).

The slower development of change in mean action potential duration and endocardial-epicardial conduction time was also associated with slower development of ST segment elevation in second and subsequent occlusions in those occlusions not developing gross intraventricular conduction abnor-

Table 1 *Effect of initial coronary occlusion on action potential duration and endo-epicardial conduction time*

Case no.	*Preocclusion*	*Minutes after coronary occlusion*				
	0	*1*	*2*	*3*	*4*	*5*
Action potential duration						
1	220	220	150	140	100	100
2	150	130	105	150	160	120
3	190	110	100	*		
4	180	140	150	150	170	155
5	190	130	80/140†	*		
6	190	150	120	115/160†	90/160†	*
7	155	98	85/120†	*		
8	185	175	120	120/140†	*	
Mean ± SEM	182 ± 8	140 ± 13	113 ± 9			
Endocardial-epicardial conduction time						
1	28	32	48	90	80	25
2	20	28	42	60	110	80
3	27	27	62	*		
4	20	20	24	30	32	33
5	24	44	100	*		
6	20	28	160	165	168	*
7	28	58	75	*		
8	26	28	52	68	*	
Mean ± SEM	24 ± 1	38 ± 5	71 ± 17			

*Onset of ventricular fibrillation.
†In these cases, alternans of the action potential occurred. The upper and lower limits are shown.

Table 2 *Effect of successive coronary occlusions on action potential duration, endocardial-epicardial conduction time, and incidence of ventricular fibrillation*

Occlusion no.	*Preocclusion*	*Minutes after coronary occlusion*				
	0	*1*	*2*	*3*	*4*	*5*
Action potential duration						
1	182 ± 8	140 ± 13	113 ± 9			
2	185 ± 8	157 ± 12	143 ± 9			
3	191 ± 8	170 ± 8	147 ± 6	136 ± 7		
4	190 ± 9	169 ± 8	140 ± 5			
5	188 ± 12	177 ± 13	153 ± 9			
Endocardial-epicardial conduction time						
1	24 ± 1	38 ± 5	71 ± 17			
2	24 ± 2	29 ± 4	51 ± 6			
3	25 ± 1	27 ± 1	49 ± 5	68 ± 5		
4	25 ± 1	28 ± 1	51 ± 6			
5	24 ± 2	28 ± 3	44 ± 9			
No. of animals with ventricular fibrillation						
1	—	—	1	3	4	5
2	—	—	—	2	2	3
3	—	—	—	—	3	4
4	—	—	—	1	2	4
5	—	—	—	1	3	4

Mean ± standard error of mean values from 8 dogs are shown.

mality. A representative example of change in mean ST segment elevation is produced in Fig. 3.

ONSET OF VENTRICULAR FIBRILLATION

Ventricular fibrillation followed in 5 of 8 dogs at a mean time of 3 minutes 23 seconds after the first occlusion and 4 minutes 44 seconds after the second occlusion. It developed in only 4 dogs after 3rd and 4th occlusions (mean times of onset 4 minutes 6 seconds, 3 minutes 33 seconds). In each case, this arrhythmia was preceded by the development of action potential alternans—both duration and amplitude. These changes were accompanied by epicardial and by endocardial ST segment alternans (Fig. 1), and by varying degrees of conduction blocks with either 2:1, 3:1, or more irregular patterns of endocardial-epicardial conduction block.

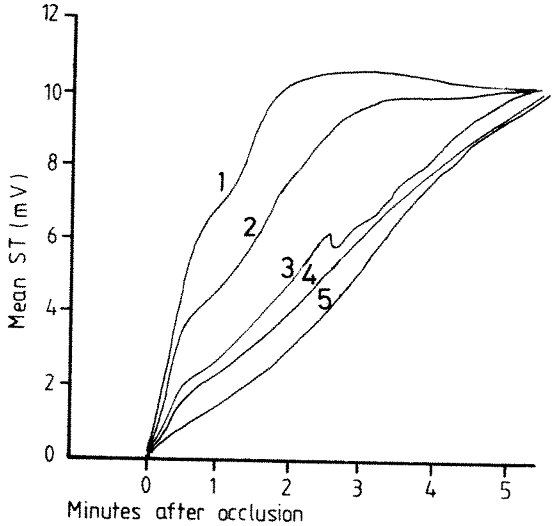

Fig. 3 *Effect of successive high coronary arterial occlusions on mean epicardial ST segment elevation in one dog. Data processed by an ST segment computer.*

The temporal relations between changes in mean action potential duration, endocardial-epicardial conduction time, and electrical alternans or conduction block before development of ventricular fibrillation are shown in Fig. 4. Data are taken from 20 occlusions in 5 dogs all resulting in ventricular fibrillation. Ventricular fibrillation was never seen without shortening of mean action potential duration and lengthening of endocardial-epicardial conduction time. Electrical alternans was seen in 19 instances (95%) and conduction block in 13 (65%).

By contrast during occlusions not resulting in ventricular fibrillation, electrical alternans was observed in 72 per cent and conduction block in 33 per cent of instances during the 5-minute occlusion period. The mean time of onset of alternans was 3 minutes 12 seconds and block 4 minutes 8 seconds compared with 2 minutes 24 seconds and 2 minutes 48 seconds, respectively when ventricular fibrillation developed.

EFFECT OF HEART RATE

Controlled heart rates from 100 to 200 beats/minute were achieved with combined atrial pacing and

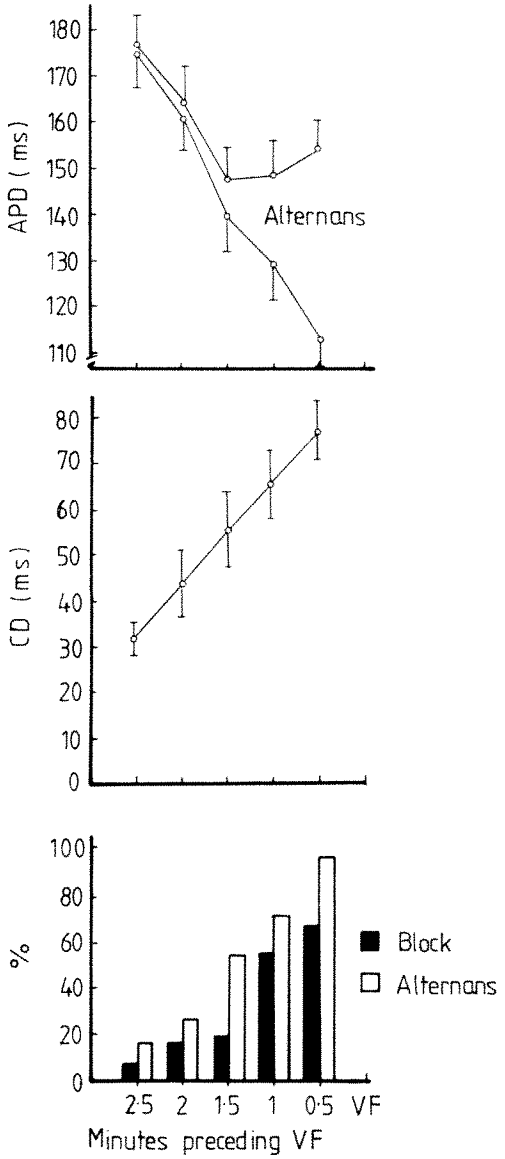

Fig. 4 *Changes in action potential duration, conduction delay, and frequency of AP alternans and block before onset of ventricular fibrillation. The two values of APD refer to alternating values.*

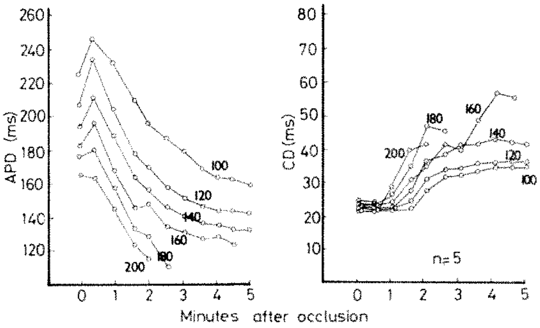

Fig. 5 *Effect of increasing heart rate in second and subsequent coronary occlusions in 5 dogs on APD and CT. Note the initiation of VF at higher rates.*

vagal stimulation, during occlusions 2 to 7 in 5 dogs. In every case control mean action potential duration was physiologically dependent on the heart rate, that is mean action potential duration before occlusion was shorter at faster heart rates. After coronary occlusion at slower heart rates, transient lengthening of the action potential duration was seen in every case. This was maximal at a heart rate of 100 beats/min where, after 30 seconds, mean action potential duration increased from 224 ± 35 to 245 ± 41 ms. After 1 minute, mean action potential duration shortened and endocardial-epicardial conduction time lengthened, as in the constant heart rate study, but the rate of progression became faster as the heart rate was increased with later occlusions. This was in contrast to the controlled rate study where changes tended to become milder with successive occlusions.

Mean ST segment elevation similarly showed progressively larger values with increase in heart rate. After 2 minutes of occlusion mean ST was 1·5, 2·1, 2·6, 4·8, 6·2, and 6·0 at 100, 120, 140, 160, 180, and 200 beats/minute, respectively.

Ventricular fibrillation was not seen at heart rates of 100 to 140 beats/min but occurred in 1 dog at 160 beats/min, 2 dogs at 180 beats/min, and 3 dogs at 200 beats/min.

These data are illustrated in Fig. 5.

Discussion

These studies show quantitatively the rapid electrophysiological changes occurring at myocardial cellular level, which precede the development of early ventricular fibrillation during acute myocardial ischaemia and amplify findings briefly described in a preliminary communication from our laboratory (Russell *et al.*, 1977). These changes are characterised by shortening of the action potential, prolongation of endocardial-epicardial conduction delay, and the appearance of potentials of 'slow response' type morphology. In addition, they are shown to be less severe during second and subsequent periods of ischaemia and at slower heart rates.

Direct recording of transmembrane action potentials in the beating heart was performed using floating microelectrodes. We have modified previously reported techniques (Woodbury and Brady, 1956; Prinzmetal *et al.*, 1962; Czarnecka *et al.*, 1973) to permit more stable recordings from ischaemic myocardium in vivo. Restriction of cardiac movement by a metal ring to protect electrode impalement was not required since the fine distal tip of the electrode was supported proximally by a wedge of thicker glass. The problem of myocardial splinting causing alterations of regional blood flow was thus avoided. Measurements of absolute membrane transmembrane potential and upstroke velocity were not performed in our experimental preparation because of tip movement artefact and intermittent incomplete cellular impalement.

The effect of anoxia and ischaemia in shortening the action potential and decreasing its amplitude is well known (Trautwein *et al.*, 1954; McDonald and McLeod, 1973). These changes were clearly shown in the present study but occurred more rapidly than in previously reported in vitro studies of anoxic myocardium or isolated perfused pig hearts (Downar *et al.*, 1977b) and were particularly prominent after coronary occlusions that eventually resulted in ventricular fibrillation. For example, action potential duration after 3 minutes of ischaemia was 50 to 60 per cent of control and comparable to the degree of shortening achieved after 30 minutes of anoxia in isolated ventricular muscle preparations. This action potential shortening during ischaemia is thought to result from diminished energy-dependent calcium slow-flux under conditions of reduced ATP availability of adenosine triphosphate and to reflect the abnormal energy balance within ischaemic tissue (McDonald and McLeod, 1973). At slower heart rates, and therefore presumably with milder ischaemia, transient prolongation of the action potential was often noted during the initial 30 seconds after coronary occlusion. This effect after acute ischaemia could be related to the greatly prolonged potentials shown in chronically ischaemic conduction tissue (Friedman *et al.*, 1975).

The induction of 'slow response' type morphology potentials within 3 minutes of ischaemia presumably results from inactivation of rapid inward sodium current after rapid loss of membrane potential (Weidmann, 1955). Membrane depolarisation during ischaemia has been described in the dog (Samson and Scher, 1960; Prinzmetal *et al.*, 1962) and in the pig heart (Kléber *et al.*, 1978) and related to TQ segment depression of the extracellular electrogram. A loss of action potential amplitude was observed in our series though not quantified, which is consistent with these observations. This contrasts with findings during in vitro studies of anoxic myocardium that have demonstrated gross shortening of action potential but with maintenance of transmembrane resting potential. Slowing of intramyocardial conduction particularly between endocardium and epicardium during ischaemia is well described (Durrer *et al.*, 1971, Cox *et al.*, 1973) and has also been ascribed to the development of 'slow potentials' (Cranfield *et al.*, 1972). In the present study, action potentials with a morphology similar to these slow response potentials were associated with pronounced conduction delays of 50 to 150 ms.

Alternans both of amplitude and of duration of the action potential was observed between 2 and 5 minutes of ischaemia and was most obvious during slow response activity. The alternans increased in magnitude with time and in several dogs developed into intermittent conduction block with either a 2:1 or more irregular patterns. These changes were reflected in the surface electrocardiogram as ST segment alternans. Similar alternating phenomena have been described in ischaemia (Downar *et al.*, 1977b) and in association with arrhythmias (El-Sherif *et al.*, 1977). In our series electrical alternans of the action potential preceded ventricular fibrillation in 95 per cent of cases and epicardial conduction block preceded fibrillation in 65 per cent. Moreover, both alternans and conduction block occurred earlier and more frequently in occlusions resulting in fibrillation. Electrical alternans could arise either by a true cellular potential alternans (Kleinfeld and Stein, 1968) or by means of electrotonic interaction between adjacent areas of intermittent conduction block (Hellerstein and Liebow, 1950). An increase in diastolic excitability threshold, as may follow an increase in extracellular potassium, could account for the conduction blocks observed in this study (Elharrar *et al.*, 1977). Alternatively, a myocardial depressant factor has been isolated from ischaemic venous effluent blood with pronounced depressant effects on excitability (Downar *et al.*, 1977a). Electrical uncoupling of hypoxic or anoxic cardiac cells has been shown in vitro and may contribute to inhomogeneity of impaired ventricular conduction during ischaemia (Wojtczak, 1976). Though the association between the electrical phenomena and fibrillation is most striking it need not necessarily imply a cause and effect relation.

The presence of 'slow response' activity and distinct endocardial-epicardial conduction delays however would provide the exact setting for initiation of arrhythmias by re-entrant excitation. In addition, local heterogeneity of unidirectional conduction block may result from regional variations in diastolic excitability threshold. It is possible, therefore, that quite local discrete regional asynchrony of excitability occurring simultaneously in many regions of the ischaemic ventricle may be of importance in the initiation of ventricular fibrillation. Multifocal re-entrant excitation would then be possible in areas of myocardium of a few millimetres diameter. Abnormal automaticity which is an alternative possible mechanism has been shown in 'slow response' ventricular muscle fibres as well as in conducting tissue (Imanishi and Surawicz, 1974). No such activity however was recorded during any cellular impalement preceding ventricular fibrillation arguing against its role in early ventricular arrhythmogenesis.

Observations during later occlusions at varying heart rates confirmed the findings of other workers (Han, 1969; Kent *et al.*, 1973) that the vulnerability of the heart to ventricular ischaemia is enhanced with increasing heart rate. In the present study, ventricular fibrillation did not occur at rates below 140 beats/min. At higher heart rates the relation between earlier onset of fibrillation and more rapid changes in action potential and conduction during ischaemia is consistent with re-entrant excitation and strongly supports a re-entrant mechanism for the early phase of cardiac arrhythmias after acute myocardial ischaemia.

Another result of these studies is one of practical importance for those investigating experimental myocardial infarction in that electrophysiological measurements have been shown to be different during the first compared with subsequent occlusions. Thus, in the 5 dogs which developed ventricular fibrillation, the mean time of onset of this arrhythmia occurred 45 or more seconds earlier during the first occlusion. Similarly, after later occlusions, a slower rate of shortening of action potential and prolongation of conduction delay, together with less ST segment elevation, was observed despite comparable heart rates. These findings suggest enhanced vulnerability of the myocardium to arrhythmias during initial coronary artery occlusions and are consistent with an altered ischaemic response in the relevant area of myocardium during successive periods of occlusion. This phenomenon is compatible with the finding of diminished contractility in myocardium reperfused after transient ischaemia (5 to 10 minutes coronary occlusion) (Vatner *et al.*, 1975; Smith *et al.*, 1978). If ischaemia damages the contractile apparatus, a situation of reduced oxygen demand, and hence less oxygen debt, could then be created during a second or subsequent occlusion. Milder changes during a second or subsequent occlusion may reflect some adaptive mechanism controlling coronary blood flow and related to greater vasodilator activity consequent upon release of vasoactive adenine nucleotides (Berne and Rubio, 1969). Alternatively, depletion of noradrenaline during the first occlusion could alter the metabolic and electrophysiological responses to successive occlusions. This lack of reproducibility of electrophysiological data between the initial and subsequent periods of ischaemia indicates that studies by other workers employing similar experimental models of repetitive coronary occlusion should be critically reappraised. Comparative studies of metabolic or pharmacological intervention during ischaemia may have little validity if not performed after an initial sham occlusion.

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Truncus arteriosus communis with intact ventricular septum[1]

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SUMMARY This is the first documented case of truncus arteriosus communis with intact ventricular septum in which extensive clinical, haemodynamic, angiographic, and pathological data are available. Angiography suggested the presence of two discrete semilunar valves but necropsy showed a basically single semilunar valve.

This case fills a gap in the spectrum of aorticopulmonary, truncal, and infundibular septal defects, and reinforces the belief that the essence of truncus arteriosus communis is a single semilunar valve, common to both ventricles, which need not be associated with the defects in the adjacent parts of the structural continuum.

In the common forms of truncus arteriosus communis, as the term is used in cardiology, a single great artery arises from the heart above a single semilunar valve, gives origin in its ascending portion to coronary and pulmonary arteries, and continues as the aorta. Though an infundibular septal deficiency is not a necessary component of truncus arteriosus communis, instances of this anomaly in which the infundibular septum is intact are very rare. We are aware of no previous report describing a heart with truncus arteriosus communis and intact ventricular septum in which extensive clinical, haemodynamic, and angiographic data, as well as pathological data are available. The purpose of this report is both to describe and to discuss such a case and to comment on its implications with respect to the embryology, definition, and classification of truncus arteriosus communis.

Case history

A 3-month-old boy had been born at term by caesarean section, to a diabetic mother; his birthweight was 4252 g (9 lb 6 oz). On the second day of extrauterine life he was noticed to have a heart murmur. Mild central cyanosis and congestive heart failure were first detected at the age of 3 weeks. He had frequent respiratory infections and persistent congestive heart failure in spite of full medical treatment.

PHYSICAL EXAMINATION AT AGE 3 MONTHS

The infant was in mild respiratory distress with a respiratory rate of 60/minute. There was slight central cyanosis and no clubbing. Pulse rate was 160/minute, regular in rhythm, and bounding in form. Femoral pulses were neither diminished nor delayed. There was mild intercostal retraction on inspiration, and easily visible cardiac pulsation on the left side. The apex beat was in the 5th left interspace beyond the mid-clavicular line. There was a slapping parasternal impulse and a systolic thrill maximal in the 3rd and 4th spaces at the left sternal edge. On auscultation the first sound complex was of normal intensity. The second sound appeared to be split but a phonocardiogram was not obtained. A third heart sound was heard at the apex. A grade 4/6 harsh systolic murmur was maximal in the 3rd and 4th spaces at the left sternal edge. A grade 2/4 mid-diastolic murmur was heard at the apex. The lungs were clear. The liver was palpable 2 cm below the right costal margin.

CHEST *X*-RAY

The cardiomediastinal shadow was moderately enlarged and the pulmonary vascularity was increased.

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ELECTROCARDIOGRAM

This showed regular rhythm with a mean frontal plane QRS axis of +150°. The patterns of left atrial enlargement and combined ventricular hypertrophy were present (Fig. 1).

CARDIAC CATHETERISATION

Catheterisation at the age of 3 months (Table) showed that neither the aorta nor the pulmonary artery was entered from the right ventricle.

ANGIOCARDIOGRAMS

Injection into the root of the great artery arising from the base of the heart showed that it gave rise to the coronary, pulmonary, and systemic arteries in its ascending portion. An unopacified area at the root of this great artery, best seen in the lateral projection, was interpreted as a septum between 2 semilunar valves (Fig. 2 and 3). No reflux into either ventricle was seen.

A left ventriculogram showed opacification of the root of the great artery but not of the right ventricle.

A right ventriculogram showed opacification of the root of the great artery via a well-defined but narrow infundibulum. Opacification of the left ventricle was seen in this injection.

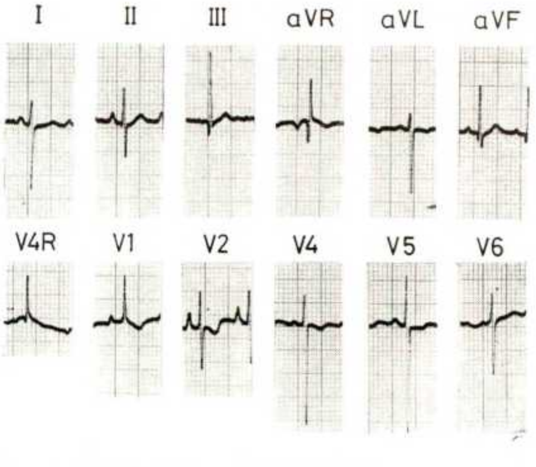

Fig. 1 *Electrocardiogram at age 3 months.*

Table *Cardiac catheterisation data at age 3 months*

Site	O_2 *saturation* (%)	*Pressure* (*mmHg*)
Superior vena cava	54	
Right atrium, high	52	
Right atrium, middle	58	a = 10 mean = 7
Right atrium, low	68	
Inferior vena cava	62	
Right ventricle	68	124/0-1
Right upper pulmonary vein	95	
Left pulmonary vein	94	
Left atrium	91	a = 15, v = 25 mean = 17
Left ventricle	89	110/0
Aorta	81	mean = 52

Note: Difference in right ventricular and left ventricular systolic pressures is consistent with lack of interventricular communication and some degree of right ventricular infundibular stenosis. Aortic pressure was overdamped. The left atrial oxygen saturation, lower than that in the pulmonary veins that were entered, is presumably caused by the perfusion of underventilated lung whose pulmonary vein was not entered. The same explanation may apply to the left ventricular saturation with the additional factor of semilunar valve regurgitation.

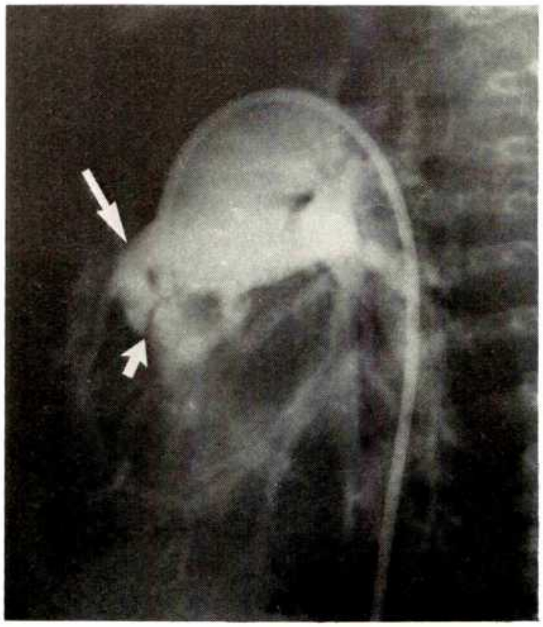

Fig. 2 *Angiogram in root of great artery showing filling defect caused by dysplastic truncal valve tissue of anterior leaflet (shorter arrow). Longer arrow indicates anterior sinus of Valsalva.*

The diagnosis of an unusual form of truncus arteriosus, or aorticopulmonary septal defect with 2 semilunar valves, was made on the basis of these data.

SUBSEQUENT COURSE

The infant continued in severe congestive heart failure with poor weight gain, and at the age of 5 months was submitted to operation. It was planned to attempt construction of separate aortic and pul-

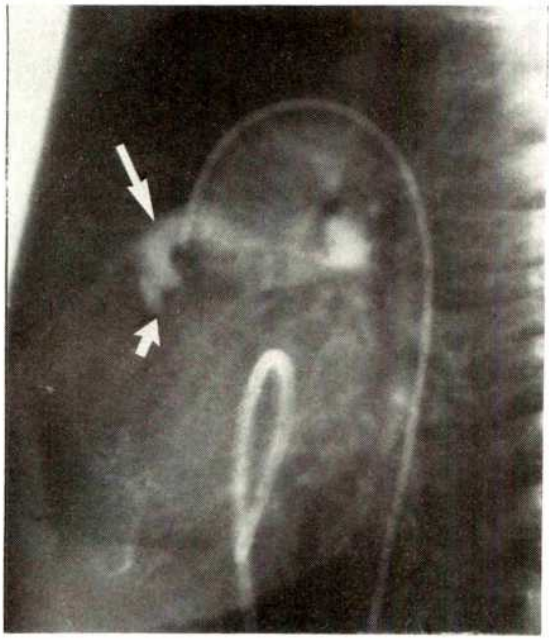

Fig. 3 *Angiogram in root of great artery showing filling defect caused by dysplastic truncal valve tissue of anterior leaflet (shorter arrow). Contrast medium is trapped in anterior sinus of Valsalva (longer arrow) giving the false impression of a rudimentary main pulmonary artery with its own semilunar valve.*

monary channels or, if this proved to be impracticable, to band the pulmonary arteries. During induction of anaesthesia he developed cardiorespiratory arrest. All resuscitative measures were unsuccessful.

NECROPSY FINDINGS

The heart was enlarged. From the base of the heart a single great artery emerged. There was hypertrophy, enlargement, and endocardial thickening of all the cardiac chambers. A patent foramen ovale was present.

The architecture of the infundibulum of the right ventricle was abnormal. The septal band group proceeded to the base and met the parietal band to form an arch. This arch, however, was somewhat narrowed superiorly. This was related to the presence of the single great artery emerging from both ventricles, straddling the ventricular septum. The valve of this artery was quadricuspid, with one each of anterior, posterior, right, and left leaflets. The right was slightly larger than the posterior leaflet which in turn was larger than the left; the anterior leaflet was the smallest. The commissure of the left and anterior leaflets was also at the anterior, right, side of the ventricular septum so that the left leaflet also bridged the ventricular septum. The crest of the muscular ventricular septum lay in the same plane as the arterial valve (Fig. 4 and 5). Valve tissue arose from this crest and was confluent, with the commissure of the right and posterior leaflets, posteriorly, and with the left leaflet, near its commissure with the anterior leaflet, anteriorly. The left leaflet close to its junction with the posterior, non-coronary, cusp was related to the mitral valve. The valve tissue was very thickened throughout, with many single and confluent nodular formations. The right coronary ostium emerged from the sinus of Valsalva of the right bridging cusp and the left coronary ostium from that of the left bridging cusp. These ostia appeared obstructed by the much thickened nodular formation of the valve tissue. This arterial trunk

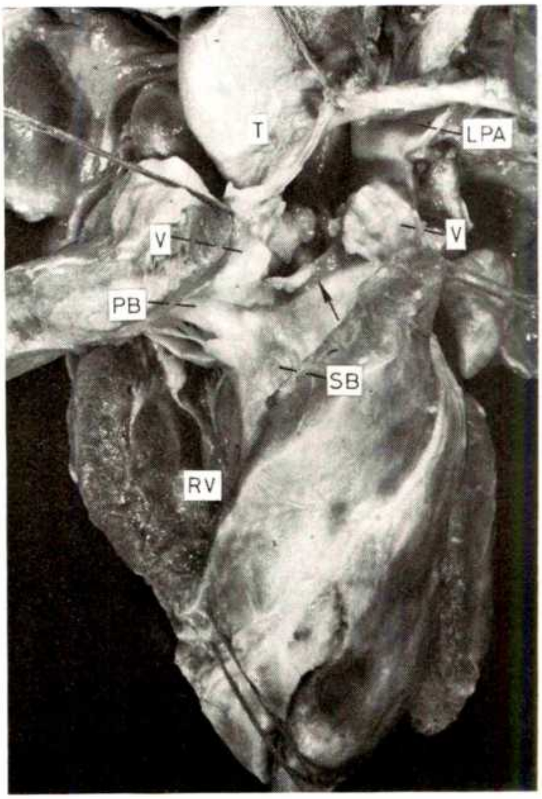

Fig. 4 *Anterior view of heart showing the outflow tract of the right ventricle. RV, right ventricle; PB, parietal band; SB, septal band; V, truncal valve; T, common arterial trunk; LPA, left pulmonary artery. Arrow points to the truncal valve tissue extending over the ventricular septum. Note the absence of a ventricular septal defect.*

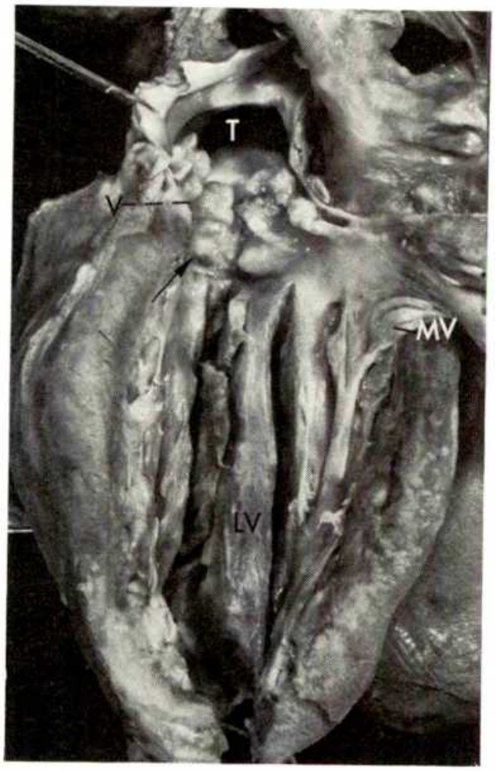

Fig. 5 *Left ventricular view: the linear cuts in the left ventricle indicating the areas from which microscopical sections were studied. LV, left ventricle; MV, mitral valve; V, truncal valve; T, common arterial trunk. Arrow points to much thickened nodose truncal valve which extends on the summit of the ventricular septum. Note the absence of a ventricular septal defect from the left ventricular view.*

gave off the pulmonary trunk anteriorly, which in turn divided into right and left pulmonary arteries. The main arterial trunk then proceeded into a left aortic arch giving off the brachiocephalic vessels.

The left coronary artery gave off 2 anterior descending branches but formed no left circumflex artery. The right coronary artery formed the posterior descending branch.

At a gross level all walls of the left ventricle on section presented a variegated picture of red and white areas. Microscopical sections through all walls of this chamber presented areas of recent and old infarction.

Aside from the findings in the heart the pathological diagnoses were partial pulmonary atelectasis, bilateral, with chronic passive hyperaemia of the lungs and liver.

Discussion

PREOPERATIVE DIAGNOSIS

In the angiocardiograms, the unusual diastolic configuration of the dysplastic tissue of the anterior truncal leaflet gave the false impression that it represented a septum separating an anterior right ventricular outlet valve from a posterior left ventricular outlet valve. Two semilunar valves were therefore believed to be present. Necropsy showed only one semilunar valve though the dysplastic tissue on the crest of the ventricular septum suggests an early stage of division into 2 semilunar valves. To avoid this angiographic misinterpretation in the future we need to remember this patient, and to recall how thick and fleshy the dysplastic valve tissue can be in truncus arteriosus communis.

SURGERY

Surgically, it seems that this heart may have been accessible to a procedure similar to that described by Daily *et al.* (1975). An eccentrically placed channel might have been created from the right ventricular outlet to the main pulmonary artery orifice without obstructing the channel from the left ventricular outlet to the aortic arch. The small size of the structures and the doubtful effectiveness of the dysplastic valve tissue at the right ventricular and left ventricular outlets after such a procedure would have made its success a considerable tour de force.

PATHOLOGY

The old and recent infarcts have not, to our knowledge, been previously described as complications of truncus arteriosus communis and may be related to the proximity of this valve tissue to the coronary orifices.

EMBRYOLOGY, DEFINITION, AND CLASSIFICATION

The remarkable thing about this case is the absence of an infundibular septal defect. In addition, though there is a clearly differentiated truncal valve with 4 circumferential leaflets, valvular tissue is also present on the crest of the septum extending across the diameter of a root of the great artery; this tissue is not formed into leaflets. Similar cases have previously been described by Bharati *et al.* (1974) and Rosenquist *et al.* (1976). We believe these features to have possible implications with respect to the embryology, definition, and classification of truncus arteriosus communis.

The definition and classification of truncus arteriosus communis are still the subject of considerable controversy. On the one hand there is the natural desire to relate postnatal appearances to prenatal development, as evidenced by the use of embryological terms to describe postnatal structures, and on the other hand the pathological embryology of these defects is not known.

The normal embryonic structures whose maldevelopment is believed to be relevant to truncus arteriosus communis are the aorticopulmonary septum, the truncus arteriosus, and that part of the partition between the right ventricular and left ventricular outflow tracts immediately below the 2 semilunar valves, which becomes the infundibular septum. The term 'truncus arteriosus communis', as used by most cardiologists, includes both the single great artery arising from the heart and the semilunar valve at the root of this great artery. Some embryologists (Van Mierop *et al.*, 1978) use the term only for the precursor of 'the truncal sinuses of Valsalva and valve cusps, *not* the common arterial trunk distal to it'; what cardiologists call the common arterial trunk is derived from the aortic sac. The ascending aorta and pulmonary artery are formed from the aortic sac when it is partitioned by an invagination of the posterior wall called the aorticopulmonary septum. This implies that defective partition into aorta and pulmonary artery would represent, embryologically, an aorticopulmonary septal defect which may or may not be associated with persistence of the embryological truncus arteriosus communis. This also means that the term aorticopulmonary septum as used by cardiologists corresponds to the embryological aorticopulmonary septum but not the embryological truncal septum. We believe a distinction has to be made between the term truncus arteriosus communis as used to describe a prenatal, embryological structure, and truncus arteriosus communis as used to describe a postnatal structure.

If the above 3 artificial subdivisions of the structural continuum always functioned, in abnormal states, as a single developmental unit, we would not need to draw any fine distinctions between one part and another for the purposes of definition and classification. However, they do not always function as a single developmental unit in abnormal states, as evidenced, for example, by our case in which infundibular septation is apparently complete, but embryonic truncal septation is incomplete.

Fig. 6 represents a spectrum of hearts previously reported to have defects in this region, including the present heart. Though this artificially arranged sequence may not correspond completely to an embryological sequence, it may clarify the problem of definition and classification of truncus arteriosus communis for the clinician and surgeon. At one end of this spectrum (Fig. 6.1) lies truncus arteriosus communis (cardiologists' term) with no main pulmonary artery (left and right pulmonary arteries arise separately), a single semilunar valve, and failure of the infundibular septum to reach the plane of the semilunar valve, leaving what is effectively a subvalvar ventricular septal defect. This corresponds to Collett and Edwards Type 3 (Collett and Edwards, 1949) and may be regarded, embryologically, as truncus arteriosus communis with associated aorticopulmonary and infundibular septal defects. In Fig. 6.2 arterial septation has resulted in the main pulmonary artery but is otherwise the same as in Fig. 6.1. Embryologically we regard Fig. 6.2 as depicting truncus arteriosus communis with an infundibular septal defect and partial absence of the aorticopulmonary septum. The heart reported here (Fig. 6.3) exemplifies a further degree of truncus arteriosus communis (cardiologists' term) in which the infundibular septum is fully formed, there is no ventricular septal defect, truncal valve tissue is present on the crest of the infundibular

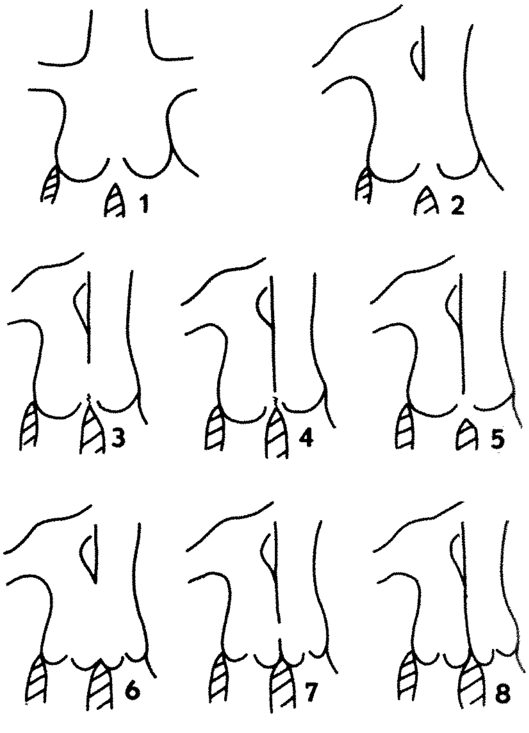

Fig. 6 *Diagrammatic representation of spectrum of hearts reported to have defects in the region of the truncus arteriosus. See text. The pulmonary artery is drawn on the right side of the aorta only because of the constraints imposed by representing 3D in 2D.*

septum, but differentiation into right ventricular and left ventricular outlet valves has not occurred. Embryologically this is truncus arteriosus communis with partial absence of aorticopulmonary septum. Fig. 6.4 represents 'pure' truncus arteriosus communis with well-formed aorticopulmonary septum, embryologically, as exemplified by case 4 of Rosenquist *et al.* (1976) and Fig. 6.5 truncus arteriosus communis with no aorticopulmonary septal defect, embryologically, but with ventricular septal defect, as exemplified by case 1 of Rosenquist *et al.* (1976) The hearts described by Bain and Parkinson (1943), Van Praagh and Van Praagh (1965) and Daily *et al.* (1975) are represented by Fig. 6.6. This seems to correspond to another degree of defect in which there is little aorticopulmonary septation embryologically but separate right and left ventricular outlet valves have developed and there is no ventricular septal defect. The fact that 2 semilunar valves are present precludes the idea that there is persistence of the truncus arteriosus communis, as it is understood by embryologists. Until contrary data are available, it seems preferable to us to regard this kind of heart as an example of aorticopulmonary septal defect both embryologically and anatomically. The strictly arterial portion of these hearts is indistinguishable to us from those represented by Fig. 6.2 and 6.3. Finally (Fig. 6.7), aorticopulmonary septation progresses to the point at which the abnormality would clearly be regarded as an aortopulmonary window by the cardiologist and would correspond to an aorticopulmonary septal defect embryologically. Fig. 6.8 represents the normal.

It seems that though most instances of truncus arteriosus communis have both infundibular and aorticopulmonary septal defects as part of the complex from the embryological standpoint, suggesting a high degree of interdependence between these artificial subdivisions of the structural continuum, in rare instances, as exemplified both by this and other reported cases, one or both of these associated defects may be absent.

We believe that there are sound reasons, both embryological and surgical, for regarding aortopulmonary window, or any other instances of incomplete differentiation into ascending aorta and pulmonary artery, with 2 semilunar valves, as representing aorticopulmonary septal defect rather than a variant of truncus arteriosus communis. Edwards (1976) and Crupi *et al.* (1977) have reached the same conclusion, but whereas they regard a single semilunar valve as an essential *part* of the truncus arteriosus we prefer the perspective of Van Mierop *et al.* (1978) that the single semilunar valve is the *only* essential for truncus arteriosus.

We are grateful for the assistance of Drs Gertrude Novak, Avinash Mondkar, and Constantine Tatooles.

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Case reports

British Heart Journal, 1979, **42**, 103-105

Aortic valve replacement in a case of Ehlers Danlos syndrome

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SUMMARY A case of Ehlers Danlos syndrome is described in a 54-year-old Caucasian male. He had calcific aortic valve disease and dilatation of the ascending aorta. An aortic valve replacement was performed using a Starr prosthesis.

The rare inheritable disease of connective tissue—the Ehlers Danlos syndrome—was first described in 1682 by the Dutch surgeon Job Van Meekeren (McKusick, 1972). Since that time much has been learned of the wide spectrum of the condition, and 7 distinct types of the disease have been separated on clinical, genetic, and biochemical grounds (McKusick, 1974).

The different types have varying degrees of skin hyperextensibility, easy bruising, and abnormally mobile joints. Inheritance is variable, but specific patterns occur in several types, in some of which definite biochemical abnormalities can be found (Pinnell *et al.*, 1972; Lichtenstein *et al.*, 1973; Sussman *et al.*, 1974; Di Ferrante *et al.*, 1975; Pope *et al.*, 1975).

Surgery has always presented a problem in the Ehlers Danlos syndrome because incisions tend to widen spontaneously, sutures may tear out, and there is often great difficulty in haemostasis. The degree of risk varies between the types, and cardiac surgery has only been attempted on rare occasions. Fantl *et al.* (1961) described the repair of a partial, persistent, atrioventricular canal and clefts in the tricuspid and mitral valves in a boy of 11 with only mild features of the syndrome, and Frieden *et al.* (1962) reported a patient who died after an operation to repair ruptured aortic valve cusps.

We report the successful replacement of a stenotic aortic valve by a Starr-Edwards prosthesis in a patient with type II Ehlers Danlos syndrome, a mild classic form of the disorder.

Case report

The patient was a 54-year-old Caucasian male executive who presented for a routine health examination. He had been noted to bruise and scar excessively after minor injuries in childhood, and to have hyperextensible joints, but the condition had never worried him and he had served in the army with the Chindits.

His mother had characteristic features of Ehlers Danlos syndrome, his brother had the disease and had 2 affected children, but his sister was normal. The patient's adult medical history was relatively uneventful, though 3 years previously he had been found to have glaucoma, which was treated medically, and he had also developed a hydrocele. He had no symptoms related to the heart or cardiovascular system, and he led an active life.

On physical examination he measured 5 feet 10 inches, weighed 153 lb (69·40 kg), and had a normal physique. There were no features suggestive

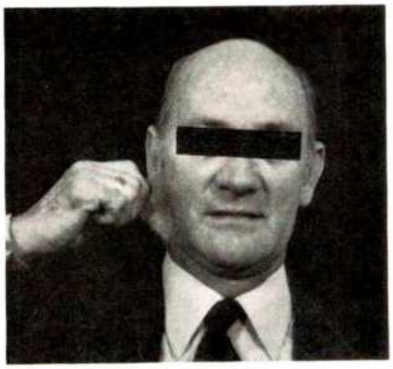


Fig. *The skin of the patient's neck is unduly easily stretched.*

of Marfan's syndrome. The skin of his forehead was deeply puckered, his ears were hyperextensible, and there were redundant folds of skin on his knees and elbows with ecchymoses and characteristic papyracious scars but no pseudotumours were evident. In general his skin had a soft velvety texture and it was excessively stretchable but not lax (Fig.). The joints of his fingers could be bent backwards but the larger joints were normal. The heart was enlarged and a soft thrill was palpable in the aortic area. The first and second heart sounds were soft, and a harsh, short, aortic, ejection systolic murmur followed by a soft early diastolic murmur was audible. The electrocardiogram showed high voltage over the left ventricle with deeply inverted T waves. Chest *x*-ray film showed an enlarged left ventricle and dilatation of the ascending aorta.

During the course of the next few months after diagnosis the patient remained free of symptoms, but his electrocardiogram deteriorated and began to show deeper ST segment depression and T wave inversion in the left chest leads. Surgical replacement of the aortic valve was advised.

Aortography was performed successfully via the right brachial artery. The vessel was delivered easily but stretched abnormally. It took sutures satisfactorily, with patency of the lumen afterwards and a good radial pulse.

At operation through a midsternal incision the left ventricle was hypertrophied and the ascending aorta showed features of post-stenotic dilatation with a narrow aortic root and expansion approximately 4 cm above the valve ring. The aortic valves were heavily calcified with a small rigid orifice and a tricuspid structure. There was no evidence of other valve lesions, but the myocardium was flabby and had a grey appearance.

Bypass was set up and the aorta was opened obliquely. An aortic biopsy was taken and the edges of the incision were excised in an elliptical fashion in order to reduce the overall diameter. The wall of the aorta was normal, and did not have the features of Marfan's syndrome. The aortic valve was excised together with the extension of calcium into the valve ring.

In view of the possible difficulties with suturing and in the interests of speed a Starr prosthesis rather than a homograft was inserted. A size 10 silastic ball prosthesis was fixed in place with runs of continuous 2/0 Prolene, interrupted at several points. Rewarming was then carried out, and the aortotomy was closed with a double running whipstitch of 4/0 Prolene. A notable feature was the difficulty in closing the short ventriculotomy stab wound in the apex, since the myocardium was soft and friable and could not retain the sutures. It was eventually necessary to close the incision over two strips of Teflon felt with multiple interrupted stitches. The aorta was similarly dealt with on removal of the aortic cannula. Heart action remained good and in sinus rhythm throughout, and final closure was routine.

The patient's postoperative progress was excellent and uncomplicated. In particular no problem of haemostasis or wound dehiscence was encountered, and healing was not delayed. After normal convalescence he resumed work 3 months later, and follow-up after one year showed that he had remained fit and well.

HISTOLOGY

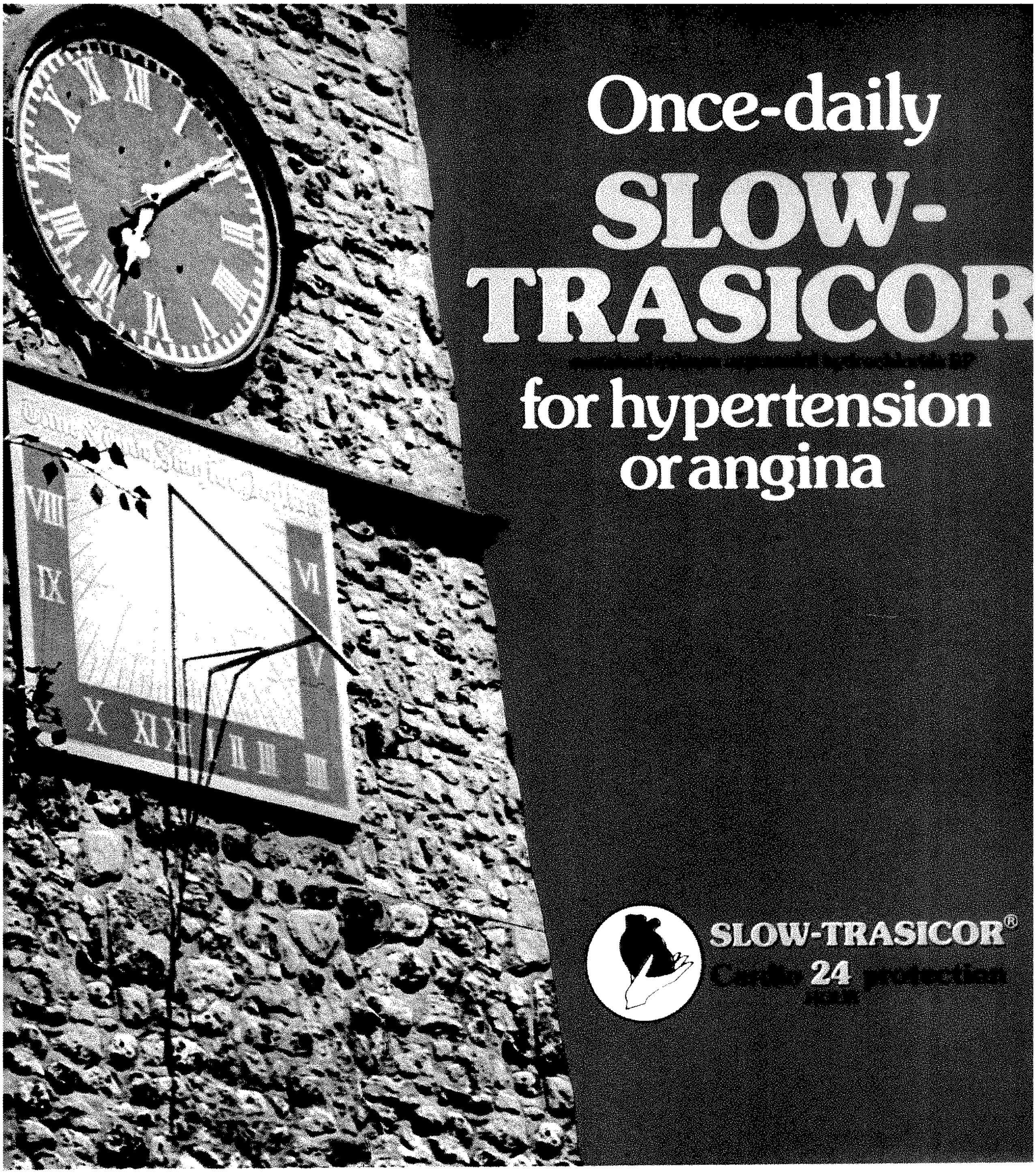
The biopsy of the aortic wall was examined independently by two pathologists, both of whom reported no microscopical abnormality in the architecture of the collagen or elastic tissue. The hydroxyproline content of the aortic biopsy was assayed and found to be 6·4 mmol/l (84 mg/100 ml) (normal 0·6-3·7 mmol/l (8-48 mg/100 ml)).

Discussion

Collagen is the most abundant protein in the human body, and in considering patients with Ehlers Danlos syndrome for surgery it is important to realise the great variability of the condition with respect to the type of connective tissue defect that may be present. Unlike Marfan's syndrome cardiac defects in Ehlers Danlos syndrome are infrequent and take no specific form (Beighton, 1970). The patient just described suffers from the type II or mild classic form of the disease, and this report is important in showing that aortic valve replacement is possible in this group when indicated.

It might have been expected on theoretical grounds that the sutures holding the prosthetic valve would tear out of the aortic ring, but this proved not to be the case, though the tissues did feel strangely soft to the needle. In contrast, closure of the incision in the cardiac muscle for the apical bypass drain presented problems because of the distinct friability of this tissue. The same property of the myocardium was reported by McFarland and Fuller (1964) in the case of a 17-year-old youth who died after spontaneous rupture of the right subclavian artery, and necropsy showed the liver, spleen, and bowel to be similarly affected. Their patient, however, had one of the more severe grades of the Ehlers Danlos syndrome.

Optimism over cardiac surgery may not, of course, be justified in the other variants of the syndrome, and especially in the more severe forms such as the



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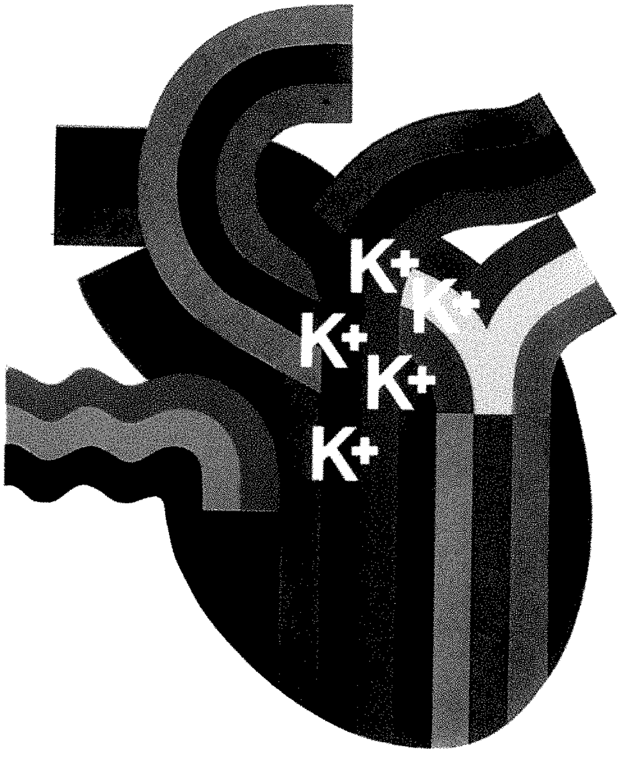

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ecchymotic and gravis types where spontaneous rupture of large arteries has often been reported (Mories, 1960; Barabas, 1967; Rybka and O'Hara, 1967). Angiography has also proved dangerous both because of bleeding at the site of the femoral puncture (Lynch *et al.*, 1965) and from the catheter itself perforating the aortic wall (Schoolman and Kepes, 1967). The future for these patients lies in obtaining a clearer understanding of the biochemistry of collagen and its ultrastructure, with the hope that pharmacological control of its biosynthesis may be possible. Work along these lines using tissue cultures is already proceeding in some centres, but at present it is not possible to achieve results in animals or man without harmful side effects (Kivirikko and Risteli, 1976).

The authors thank Dr E. Olsen, The National Heart Hospital, London W1 for reviewing the histology of the aortic tissues.

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British Heart Journal, 1979, **42**, 106-109

Uncontrolled ventricular rate in atrial fibrillation
A manifestation of dissimilar atrial rhythms[1]

CARL V. LEIER, THOMAS M. JOHNSON, AND RICHARD P. LEWIS

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SUMMARY A patient with coarse atrial fibrillation and a rapid ventricular response developed periods of high grade atrioventricular block interspersed with periods of rapid ventricular conduction after the administration of digitalis and propranolol. Intracardiac atrial recordings showed dissimilar atrial rhythms of high right atrial flutter and left atrial fibrillation. The low right atrial recordings showed flutter during the periods of fast ventricular rates and fibrillation during periods of slower ventricular rates.

Atrial fibrillation is a rhythm in which the ventricular response is usually well controlled at the atrioventricular node level with digitalis or propranolol. Inability to control the ventricular rate is not an uncommon problem and is usually explained on the basis of inadequate digitalis or propranolol dosage, an increase of the sympathetic tone (or decreased parasympathetic tone) on the atrioventricular node, an inordinately short atrioventricular node refractory period, or an accessory atrioventricular conduction pathway (Schamroth, 1971). We report a patient who presented with atrial fibrillation and a poorly controlled ventricular response. The unique findings of her electrophysiological study are the basis of this report.

Case report

A 33-year-old woman presented with increasing shortness of breath and a rapid irregular pulse. At age 8 she experienced an episode of acute rheumatic fever. Because of dyspnoea on exertion and easy fatigability, cardiac catheterisation was performed in 1969 when she was 22 years old, and moderate mitral regurgitation, moderate mitral stenosis, and trivial aortic regurgitation were demonstrated. Her mitral valve was replaced with a Starr-Edwards prosthesis, and her clinical condition improved. Over the subsequent 7 years, she reverted from sinus rhythm to atrial fibrillation three times, despite the chronic administration of antiarrhythmic agents. Each time she was successfully cardioverted back to sinus rhythm. The recent development of a rapid irregular pulse and progressively worsening shortness of breath began one week before admission. Her treatment consisted of digoxin, 0·25 mg orally daily, and warfarin sodium.

The physical examination at admission disclosed a praecordial auscultatory heart rate of 170/minute and an irregular radial pulse of 110/minute. Supine right arm blood pressure was 190/60 mmHg. No discernible jugular venous pulsations were noted. The intensity of the prosthetic opening and closing sounds was diminished because of the tachycardia. A grade 2/6 crescendo-decrescendo blowing systolic murmur was present along the left sternal border and at slower rates, a grade 2/6 decrescendo aortic regurgitation murmur was present in the same location.

The chest *x*-ray film (posteroanterior and left lateral projections) showed mild cardiomegaly, left atrial enlargement, and pulmonary vascular redistribution. The echocardiogram showed normal prosthetic valve motion, with a poppet excursion of 1 cm and an S2-opening click interval of 90 to 110 ms. Coarse atrial fibrillation was noted during transient slowing of the heart rate on the scalar electrocardiogram.

The hospital course was characterised by considerable difficulty in bringing the ventricular rate into an acceptable range. A total of 0·375 mg digoxin was administered orally over the first 12 hours, attaining a serum level of 1·3 ng/ml (1·66 nmol/l) (normal range: 0·8 to 2·4 ng/ml (1·02 to 3·07 nmol/l)). Between 12 and 24 hours after admission the rhythm continued as coarse atrial fibrillation; however, the ventricular response

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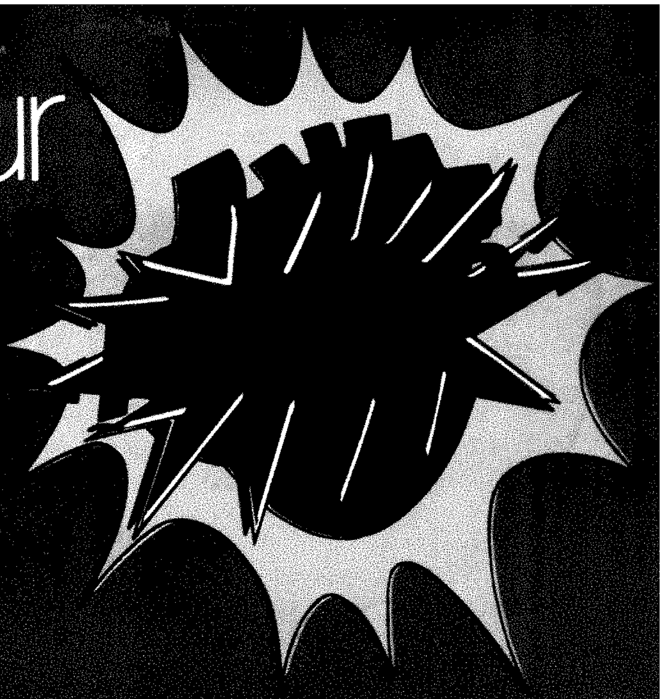
[1] Supported by a grant from the Central Ohio Heart Chapter of the American Heart Association.



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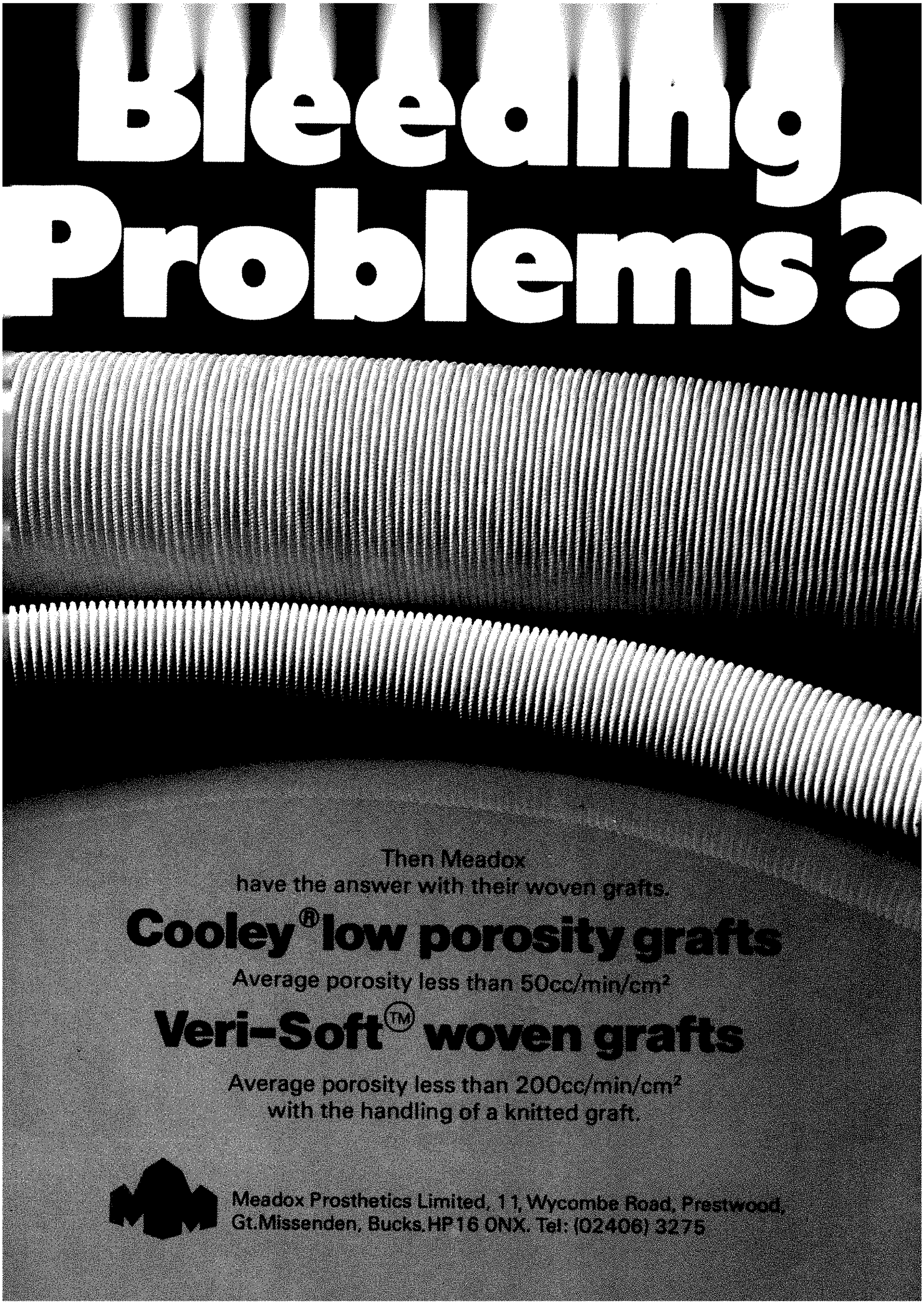

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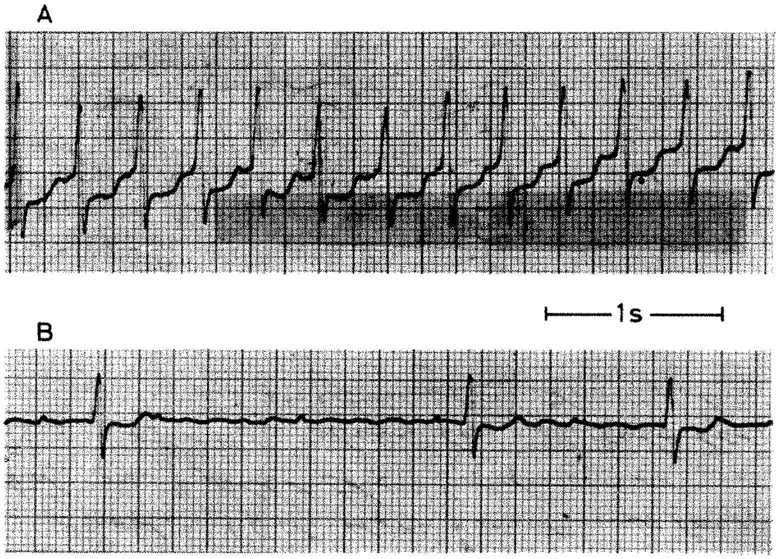

Fig. 1 *Sample monitor electrocardiographic tracings obtained after the administration of digoxin. The ventricular response of A is rapid (rate: 160-180/minute) and somewhat regular. Fifteen seconds later, the ventricular response decreased dramatically and became irregular as noted in recording B.*

underwent wide fluctuations ranging from 180/minute down to 30/minute (Fig. 1). During the periods of fast ventricular response, the patient developed dyspnoea and near syncope. Increasing the digitalis dosage (or administering propranolol) episodically decreased the ventricular response to less than 30/minute, and decreasing the dosage resulted in sustained periods of tachycardia (160 to 170/minute). This therapeutic dilemma prompted the performance of an electrophysiological study in order to determine if atrial events were in part responsible for the wide variation of ventricular rates and for the inability to decrease the ventricular rate without evoking periods of distinct bradycardia.

ELECTROPHYSIOLOGICAL STUDY AND RESULTS

Two bipolar electrode recording catheters were introduced into the right antecubital vein, and were placed in the right atrium under fluoroscopy. One catheter was positioned in the high right atrium and the other in the medial aspect of the low right atrium, adjacent to the tricuspid valve. These catheters provided electrograms of the high right atrium and the low right atrium. An oesophageal bipolar electrode catheter was positioned at the level of the mid-left atrium for recording left atrial electrograms (Barold, 1972). The signals were amplified and recorded in a frequency range of 30 to 500 cycles/second by an Electronics for Medcine DR-12. Scalar electrocardiographic leads I, aVF, and praecordial V1 were recorded simultaneously with the atrial electrograms.

The left atrial electrogram showed rapid irregular potentials, consistent with fibrillation, throughout the study. The simultaneous high right atrial recordings showed the presence of rapid regular deflections (rate 335 to 340/minute) characteristic of atrial flutter. The low right atrial recordings were of particular interest in that the rhythm in the low right atrium fluctuated between fibrillation and flutter (Fig. 2a and b). The ventricular rate during the low atrial flutter was rapid (150 to 170/minute) and during low atrial fibrillation was considerably slower (50 to 100/minute). Attempts to pace the right atrium into persistent fibrillation were not successful.

After refusing cardioversion, three doses of quinidine sulphate (300 mg orally every 6 hours) were administered in an attempt to convert the arrhythmia to sinus rhythm. She developed salvos of ventricular tachycardia and gastrointestinal distress with the quinidine and this treatment had to be discontinued. Because of the inability to convert the flutter-fibrillation to sinus rhythm, an alternative treatment was devised. A ventricular demand pacemaker was inserted into the right ventricle and digitoxin 0·1 mg orally daily and

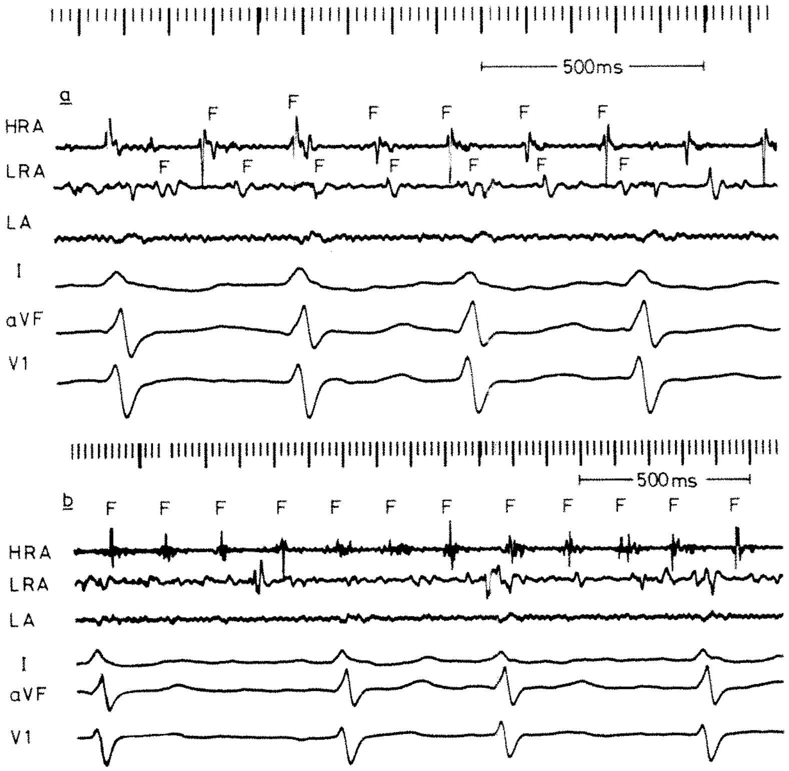

Fig. 2(a) *Right and left atrial electrograms taken during the rapid ventricular response. The left atrial (LA) recording shows fibrillation and both high right atrium (HRA) and low right atrium (LRA) show a regular tachysystole-atrial flutter. F = flutter waves.* (b) *Right and left atrial electrograms obtained during a slower ventricular rate. The high right atrium (HRA) recording shows atrial flutter and the left atrium (LA) shows fibrillation. The low right atrium (LRA) at this time shows the irregular rapid rhythm of fibrillation.*

propranolol 40 mg orally every 6 hours was administered. The digitoxin and propranolol maintained the resting heart rate at less than 100 beats per minute and the pacemaker intervened at ventricular rates less than 70/minute. During a 3-month follow-up, there was considerable improvement of the patient's dyspnoea and fatigability.

Discussion

This study shows that inadequate control of the ventricular rate during atrial fibrillation may be on the basis of dissimilar atrial rhythms. The right atrial flutter became problematic in this patient only when the flutter extended into the low right atrium—atrioventricular node region. During the periods of low right atrial flutter the ventricular rate tended to become regular and increased considerably, and during fibrillation the ventricular response decreased and became irregular. The QRS configuration during the rapid ventricular rate was similar to that during the slow rates, suggesting that a bundle of Kent accessory pathway did not account for the rapid conduction, though an atrioventricular node bypass fibre (James fibre) cannot be excluded. However, the ability to block the atrioventricular conduction with digitalis and propranolol makes the presence of an atrioventricular node bypass fibre unlikely. The difference in the atrioventricular node transmission is best explained on the basis of concealed conduction (Langendorf *et al.*, 1965), which is greater for the higher frequency irregular bombardment of fibrillation than for slower regular impulses of flutter. The atrioventricular node conduction of the two arrhythmias was strikingly different and virtually made it impossible pharmacologically to block the rapid conduction of flutter without severely blocking

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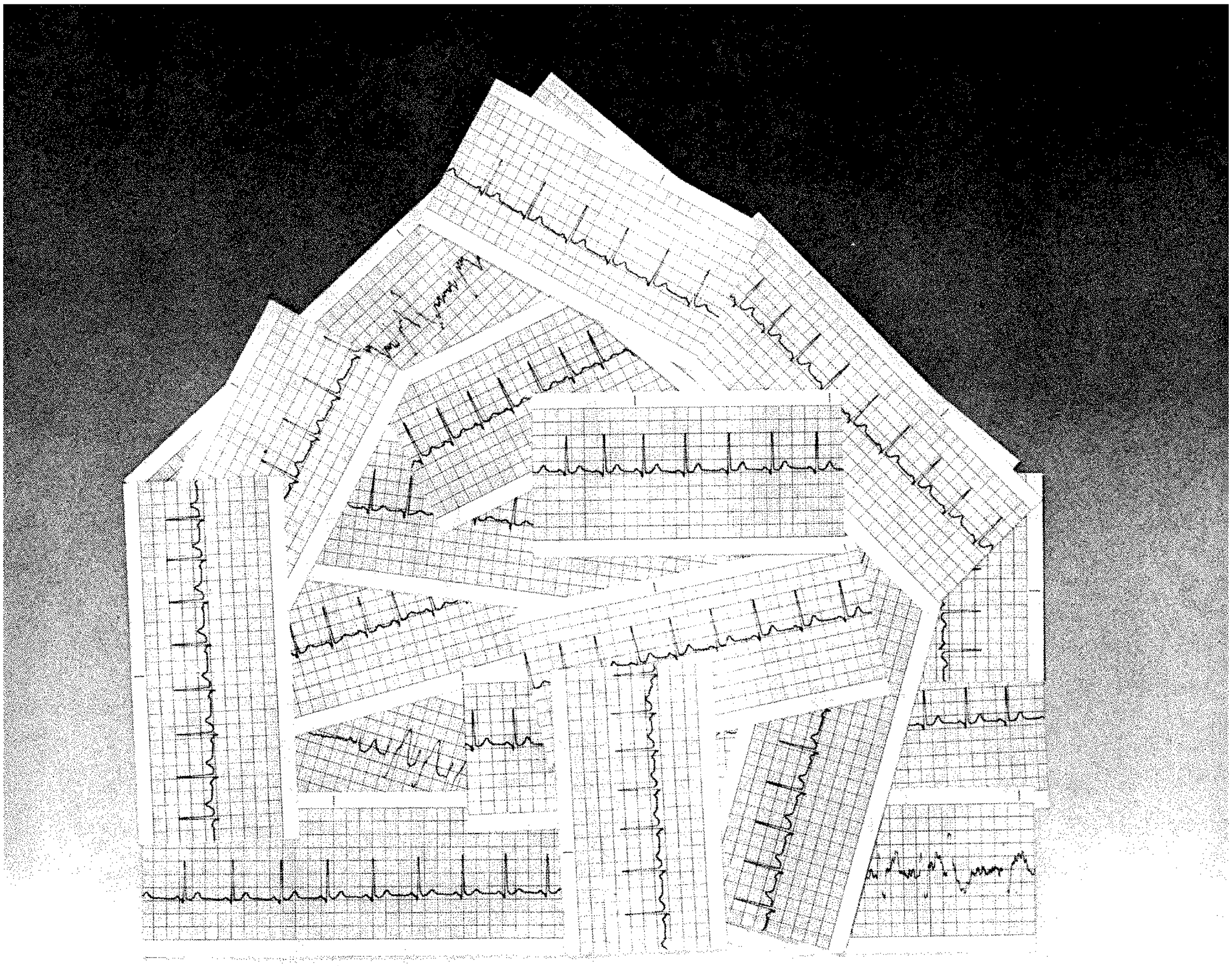

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atrioventricular node conduction during the periods of low right atrial fibrillation.

Several different combinations of atrial electrical events and dissimilar rhythms may present with coarse atrial fibrillation on the scalar electrocardiogram (Zipes and DeJoseph, 1973; Leier and Schaal, 1975, 1977). It is believed that in dissimilar atrial rhythms the atrial activity of the right atrium will dictate the behaviour of the atrioventricular node and the ventricular response. The right intra-atrial dissimilar rhythms of this patient clearly showed that the rhythm in the low right atrial—atrioventricular node region determines the conduction properties of the atrioventricular node regardless of what the rhythm(s) are in the remainder of the atria. The atrial refractory period of the low right atrial region probably determined whether this area would be in flutter or fibrillation (Zipes and DeJoseph, 1973). As the refractory period shortened, the fibrillation extended from the left atrial region into the low right atrium, pushing the flutter-fibrillation interface higher in the right atrium. Reciprocally, as the low right atrial refractory period increased the flutter front moved into this region.

While there are several reasons for a rapid ventricular response during atrial fibrillation, it is apparent that dissimilar atrial rhythms with flutter or another tachysystole in the low right atrial—atrioventricular node region are another cause. Patients with coarse atrial fibrillation or flutter-fibrillation and an uncontrolled ventricular response, should undergo atrial recordings to define the atrial rhythms present, particularly in the low right atrial—atrioventricular node region. In our patient, this procedure led to the proper therapeutic approach—pacemaker placement and pharmacological atrioventricular blockade. Had pharmacological therapy alone been pursued, there may have been a fatal outcome.

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British Heart Journal, 1979, **42**, 110-112

Coronary artery spasm of different degrees as cause of angina at rest with ST segment depression and elevation

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SUMMARY Chest pain induced by ergometrine was associated with ST depression and subsequent elevation in anterior leads in a 42-year-old man suffering from angina at rest. Coronary arteriography during the attack showed that coronary arterial spasm of different degrees was responsible for chest pain and both types of electrocardiographic abnormality.

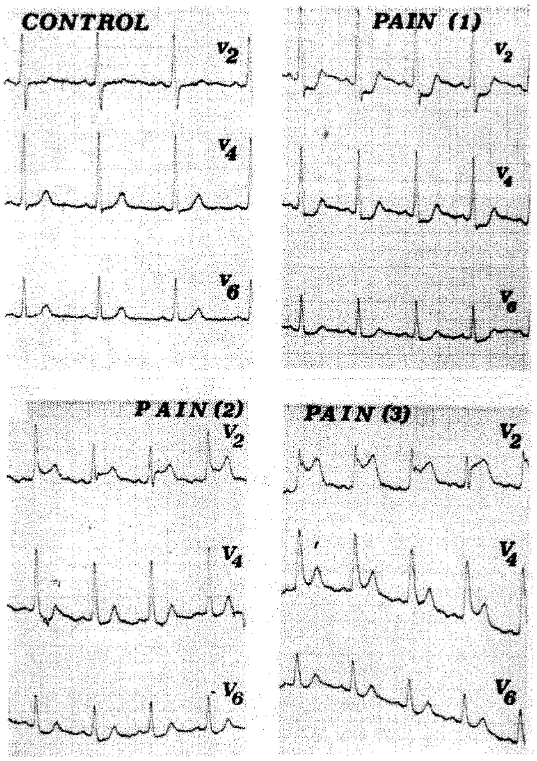

Fig. 1 *Electrocardiogram (leads V2, V4, and V6) during progressive development of chest pain associated with spasm of the left anterior descending coronary artery induced by ergometrine. Note ST segment depression in leads V2, V4, and V6 (1), and subsequent ST elevation in V2 (2), and in V2 and V4 (3).*

Although it is now firmly established that coronary arterial spasm is responsible for the severe ischaemia occurring in patients with variant angina pectoris (MacAlpin *et al.*, 1973; Oliva *et al.*, 1973; Maseri *et al.*, 1975), it is not yet clear whether or not it may also play a role in angina associated with ST depression.

We describe a patient suffering from angina at rest in whom ergometrine maleate could elicit an anginal attack associated initially with ST depression and subsequently with elevation in the same leads. Coronary arteriography performed during pain showed that coronary arterial spasm was the underlying pathogenetic mechanism of chest pain and both types of electrocardiographic abnormality.

Case report

A 48-year-old man had a 1-year history of oppressive anterior chest pain with radiation to the neck and arms. The pain occurred at rest and occasionally with exertion and was relieved by glyceryl trinitrate. The patient gave no history of hypertension or diabetes mellitus. He smoked between 10 and 20 cigarettes daily.

There was no abnormality on physical examination. Blood count, urine analysis, routine biochemical estimations, and lipid profile were normal. Chest *x*-ray film showed a normal heart size. The resting electrocardiogram showed slight depression of ST segments in leads I, II, and V1 to V3. Electrocardiogram taken during a spontaneous attack of pain showed conspicuous ST depression in leads I, II, and V2 to V6. Electrocardiogram during

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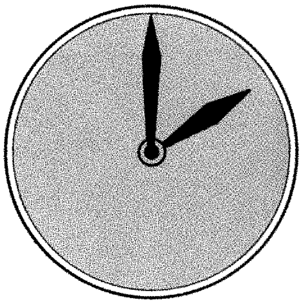

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Am. Heart J. (1976) **92,** 455, Battock DJ et al: Effects of isosorbide dinitrate and nitroglycerin on central circulatory dynamics in coronary artery disease.

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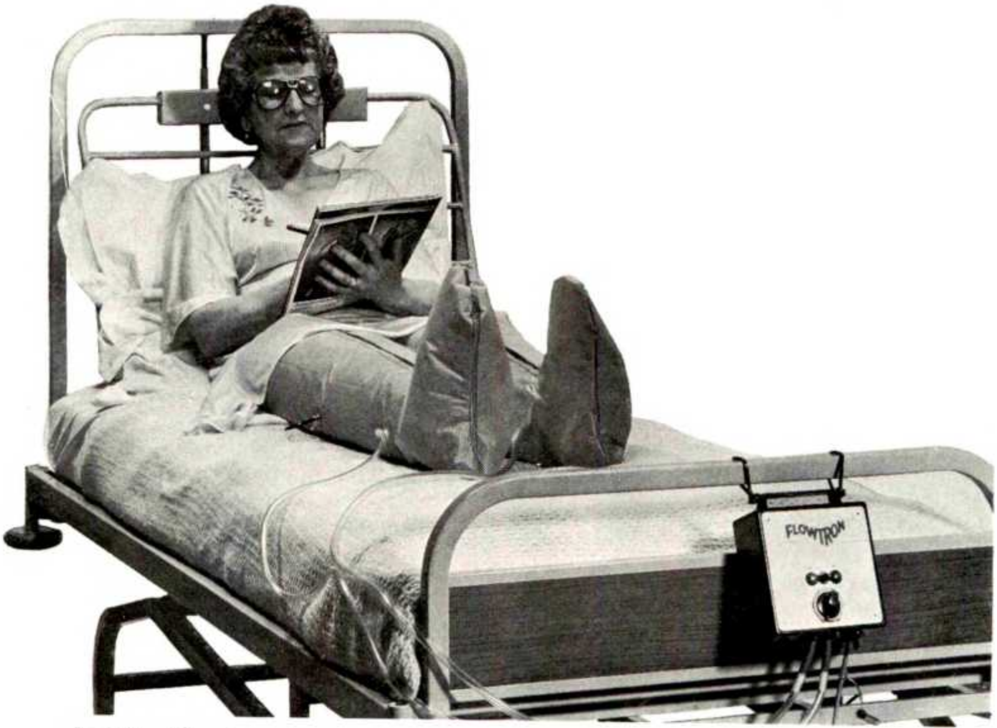

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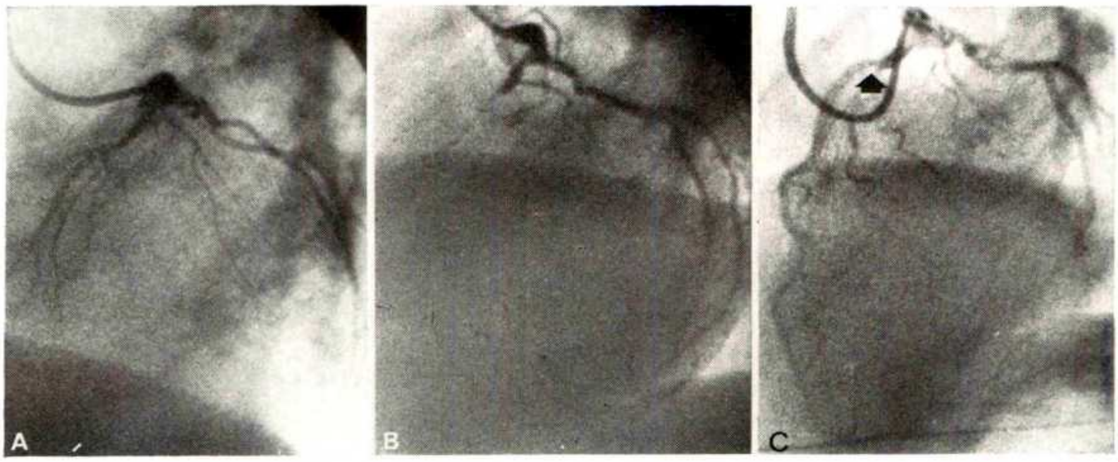

Fig. 2 *Left coronary arteriograms in the left anterior oblique projection. (A) During pain associated with ST depression. (B) During pain associated with ST elevation. (C) After the sublingual administration of glyceryl trinitrate. Note the progression of vascular spasm from A to B with occlusion of the left anterior descending coronary artery. Repeat injection after glyceryl trinitrate shows reversal of coronary arterial spasm and a mild (50%) fixed stenosis (arrow).*

a graded exercise test on a bicycle ergometer showed no ischaemic changes.

Left heart catheterisation showed pressures in the left ventricle of 120/10 mmHg and in the ascending aorta of 120/80 mmHg. Selective coronary cineangiograms obtained by the Sones technique disclosed a mild (50%) focal narrowing of left anterior descending coronary artery and a normal right coronary artery. Because the organic lesion was unlikely to have been responsible for the clinical symptoms, ergometrine maleate (0·2 mg) was administered intravenously in an attempt to provoke coronary artery spasm. Chest pain and ST depression in leads V2, V4, and V6 developed one minute after the administration of the drug. A selective left coronary artery injection during pain showed spastic obstruction without occlusion at the site of the stenosis, with slow passage of contrast medium which did not reach the apex. The chest pain persisted and the electrocardiogram now showed ST elevation in leads V2 and V4. Another left coronary artery injection at this time showed further reduction in the calibre of the left anterior descending artery and more proximal occlusion of the vessel. After sublingual administration of glyceryl trinitrate the pain subsided and the displaced ST segment returned to the isoelectric line. Left coronary arteriogram now showed no evidence of vascular spasm.

Discussion

Angina at rest may be associated with ST segment elevation or depression, and in some cases both ST elevation and at other times ST depression have occurred in the same patient (Jouve *et al.*, 1969; Maseri *et al.*, 1977a). Thallium-201 scintigraphy has shown a transmural reduction of regional perfusion during ST elevation suggesting extensive myocardial ischaemia (Maseri *et al.*, 1976), while ST depression appears to be related to subendocardial or diffuse ischaemia (Parodi *et al.*, 1977). Coronary artery spasm is accepted as the mechanism of recurrent episodes of chest pain with ST elevation, but the mechanism of rest pain with ST depression remains uncertain. However, the occurrence of coronary artery spasm has been reported in patients with subendocardial ischaemia during pain (Wiener *et al.*, 1976; Maseri *et al.*, 1977a). Marzilli *et al.* (1977) have described spasm of a small coronary artery branch or a diffuse narrowing of several branches during attacks of angina associated with ST depression.

In this patient we were able to induce an attack of angina by injecting ergometrine maleate. It is well known that this drug can provoke coronary arterial spasm and reproduce the clinical and electrocardiographic patterns of spontaneous angina (Specchia *et* al., 1976; Schroeder *et al.*, 1977). Coronary arteriography performed during the attack associated with ST depression showed spastic obstruction of the left anterior descending artery at the site of an insignificant fixed stenosis. When ST segment elevation occurred we were able to demonstrate more severe spasm which resulted in further reduction in calibre of the vessel and more proximal occlusion. The fact that spontaneous angina occurred with ST depression while the provoked attack was associated with both ST depression and elevation can be explained by the very powerful vasoconstrictor effect of the drug or by the usually prompt administration of glyceryl trinitrate at the onset of spontaneous pain.

The occurrence in this case of angina at rest with ST elevation or depression supports the hypothesis that coronary arterial spasm of differing degrees may be responsible for both types of electrocardiographic change. Thus, ST elevation and ST depression seem to represent two electrocardiographic aspects of 'the continuous spectrum of vasospastic angina' (Maseri *et al.*, 1977b).

We also reaffirm the usefulness of the ergometrine test during coronary arteriography in shedding light on the pathogenetic mechanism of angina at rest in patients who have no significant organic narrowing of coronary arteries.

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Requests for reprints to Professor Giuseppe Specchia, Divisione di Cardiologia, Policlinico S. Matteo, 27100 Pavia, Italy.

British Heart Journal, 1979, **42,** 113-115

Echocardiographic diagnosis of mobile left ventricular tumour

G. SABOT, J. M. FAUVEL, AND J. P. BOUNHOURE

From the Department of Cardiology, Rangueil Hospital, Toulouse, France

SUMMARY Echocardiography detected a mobile left ventricular tumour. The tracing showed a cluster of echoes in the left ventricular outflow tract corresponding to the location of the tumour as confirmed by cineangiograms. At operation, a thrombus was discovered, attached to a chorda tendineae.

Cardiac tumours are commonly found in the left atrium, and many reports have dealt with their ultrasonic detection in this region. Because left ventricular tumours are rare, their echocardiographic observation has been infrequent. In this report, we describe the echocardiographic features of a mobile left ventricular tumour.

Case report

This 28-year-old salesman was admitted to the Department of Cardiovascular Surgery of our hospital in January 1978, because of acute ischaemia of the right lower limb.

There was a history of an anterior myocardial infarction 5 years before admission; the coronary angiogram performed 2 months after recovery had shown a muscular bridge pattern affecting the left anterior descending coronary artery, with dyskinesia in the corresponding region of the ventricular wall. In October 1977, he suffered acute occlusion of the distal abdominal aorta necessitating thrombectomy. In November 1977, he was referred to another hospital for an acute occlusion of the right femoral artery, and embolectomy was successfully performed with a Fogarty catheter. Subsequent left heart angiography showed no filling defect; however, an operation was performed: no thrombus was found in the left ventricular cavity, but a fibrous scar was present, anteriorly located, and was partly excised. The patient recovered very well and was working until the last event.

Cardiac examination disclosed a normal apical impulse and normal first and second heart sounds; there was no gallop or murmur. The right femoral pulse was absent. The chest *x*-ray film was normal, and the electrocardiogram showed the signs of an anterior left ventricular aneurysm.

Embolectomy was again necessary, and echocardiography was performed the next day.

The recording showed a cluster of echoes in the left ventricular outflow tract, seen only during systole, between the closed mitral valve and the intraventricular septum as well as a normal left atrium, and normal mitral and aortic valve cusps (Fig. 1). These abnormal echoes were denser as the ultrasonic beam was directed more inferiorly (Fig. 2).

This finding prompted us to perform a cineangiographic study with a pulmonary arterial injection. It showed a fixed filling defect near the apex of the left ventricle, and a second mobile one was seen to move into the left ventricular outflow tract during systole and return towards the apex during systole.

With a presumptive diagnosis of left ventricular thrombus, the patient was submitted to open-heart surgery. Operation revealed 2 thrombi. A small one, the size of an olive, was attached to a chorda tendineae going from the anterior papillary muscle to the posterior one and transversely to the left ventricular cavity. The second one was larger, near the apex, with a stalk originating from a small area of remaining scar tissue around the first ventriculotomy. The 2 thrombi were removed and the fibrous tissue was completely excised. The postoperative course was uneventful and the echocardiogram was normal 4 months after operation.

Microscopical study showed a thrombus with early organisation.

Discussion

The usefulness of echocardiography in diagnosing atrial tumours was established 19 years ago by Effert and Domanig (1959). Several cases of left

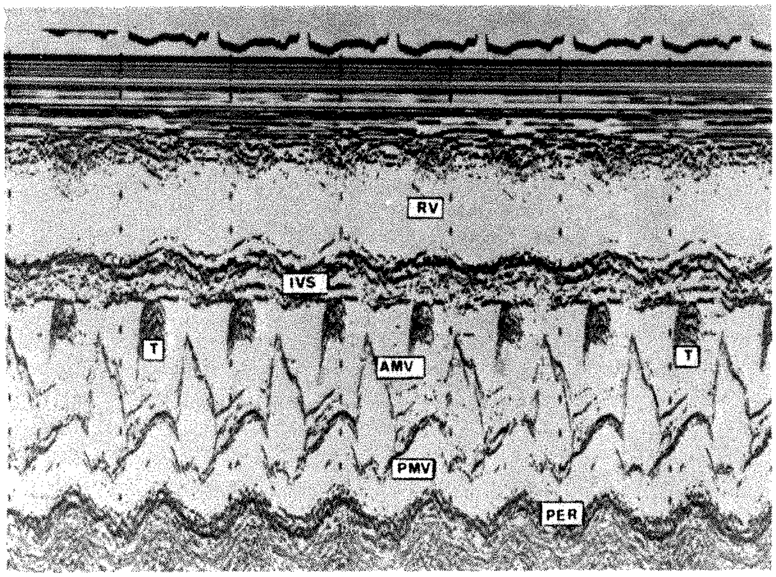

Fig. 1 *The ultrasonic beam passes through the left ventricular chamber at the level of the edges of the mitral valve leaflets. The tumour is represented by a cluster of echoes in the left ventricular outflow tract during systole. (PER, pericardium; AMV, anterior mitral valve; PMV, posterior mitral valve; T, tumour; IVS, interventricular septum; RV, right ventricle.)*

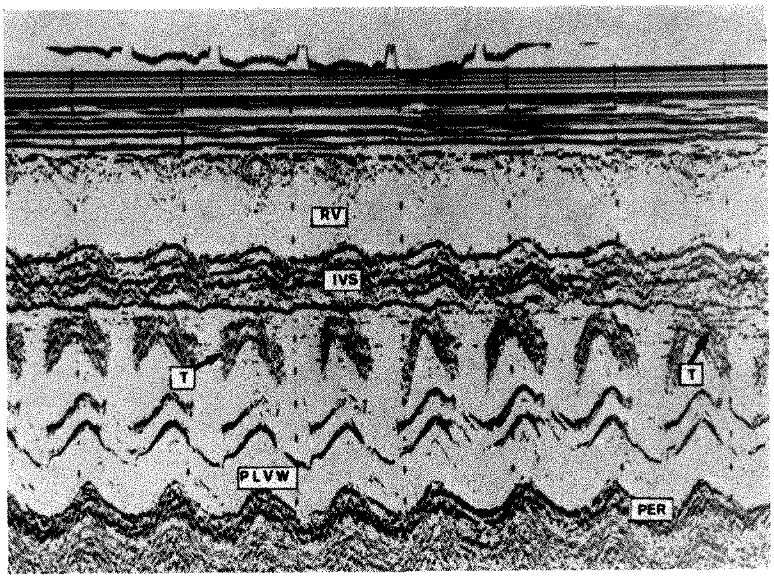

Fig. 2 *The transducer is directed towards the apex; abnormal echoes are larger, and seen only during diastole. (PLVW, posterior left ventricular wall; other abbreviations as in Fig. 1.)*

ventricular tumours diagnosed with echocardiography have been reported since 1974. Most of them were not mobile, and the echocardiographic pattern proved to be identical, whatever the tumour (rhabdomyoma, Farooki *et al.*, 1974; idiopathic calcified myocardial mass, Patterson *et al.*, 1974; alveolar rhabdomyosarcoma, Orsmond *et al.*, 1976; myxoma, Morgan *et al.*, 1977). The tracings showed a dense mass of echoes in the left ventricular chamber, anterior to the anterior mitral leaflet, and present in systole and diastole.

The tracing of our patient shows a cluster of echoes in the left ventricular outflow tract only during systole. A flail aortic valve would be visible in exactly this position, but only during diastole.

The first echocardiographic diagnosis of a mobile left ventricular tumour was reported in 1975 by Levisman *et al.* Their patient presented with multiple emboli to the brain, to the femoral artery, and to the lower peripheral arteries. The echocardiographic recording was similar to ours. Open heart surgery showed a pedunculated thrombus.

To our knowledge, our case is the second one diagnosed by echocardiography, before angiography and operation.

In patients with an unexplained thromboembolic vascular accident, echocardiography should be a useful means of detecting left heart tumours.

We are indebted to Professor A. Enjalbert for allowing us to study this patient who was under his care in the Department of Cardiovascular Surgery of the Rangueil Hospital, to Dr H. Boccalon who performed the angiographic study, and to Dr A. Cerene who operated on this patient.

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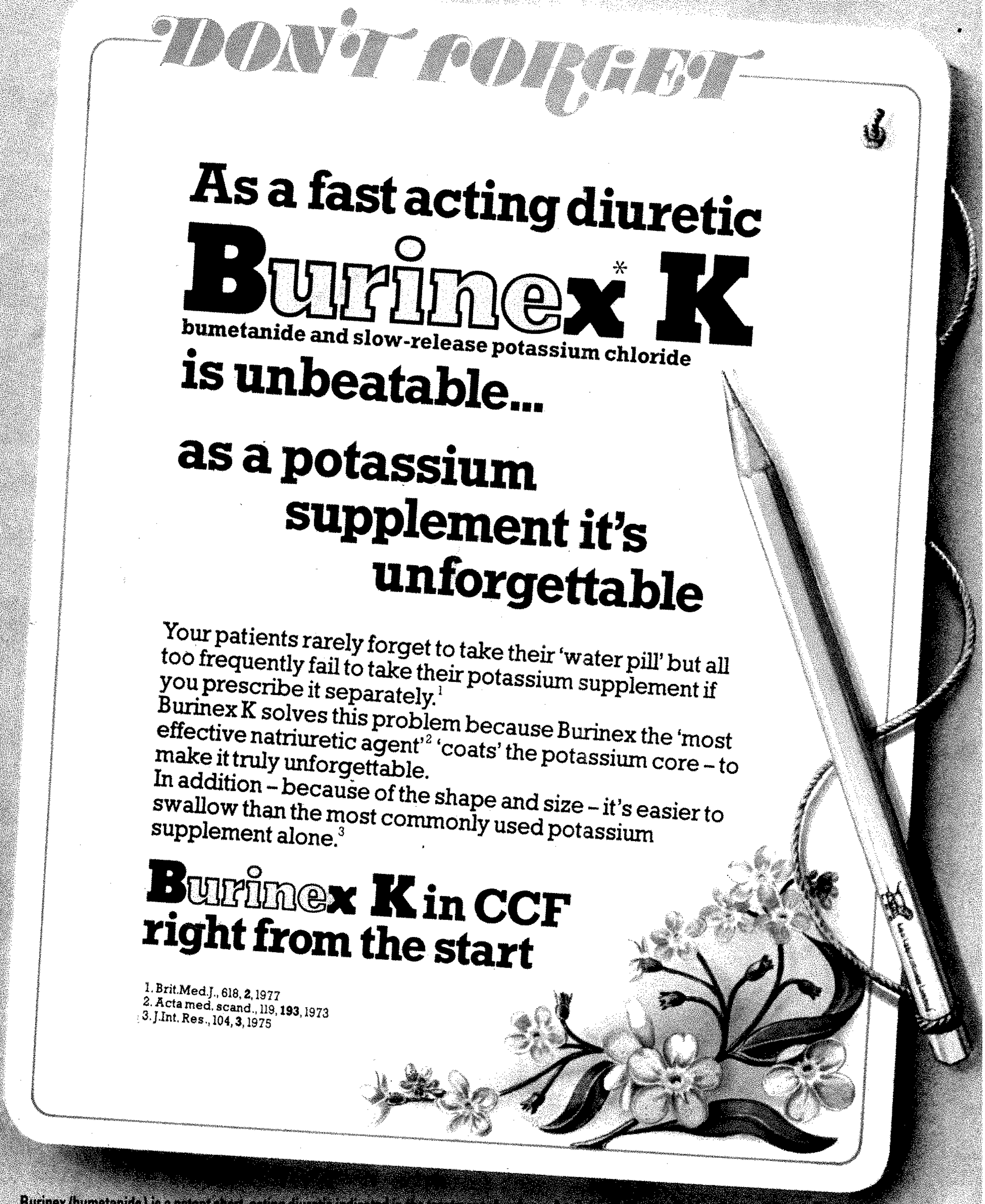

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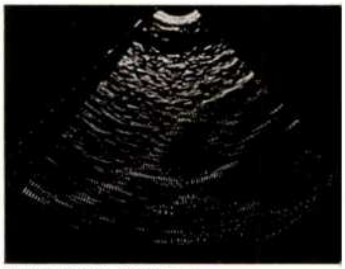

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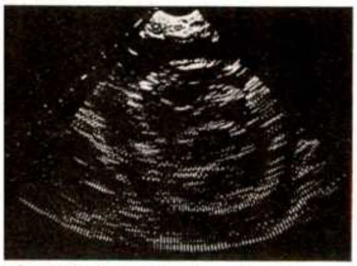

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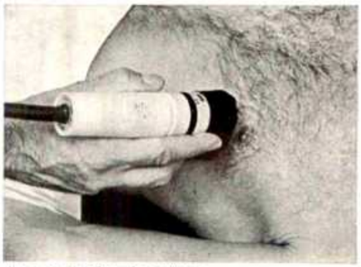

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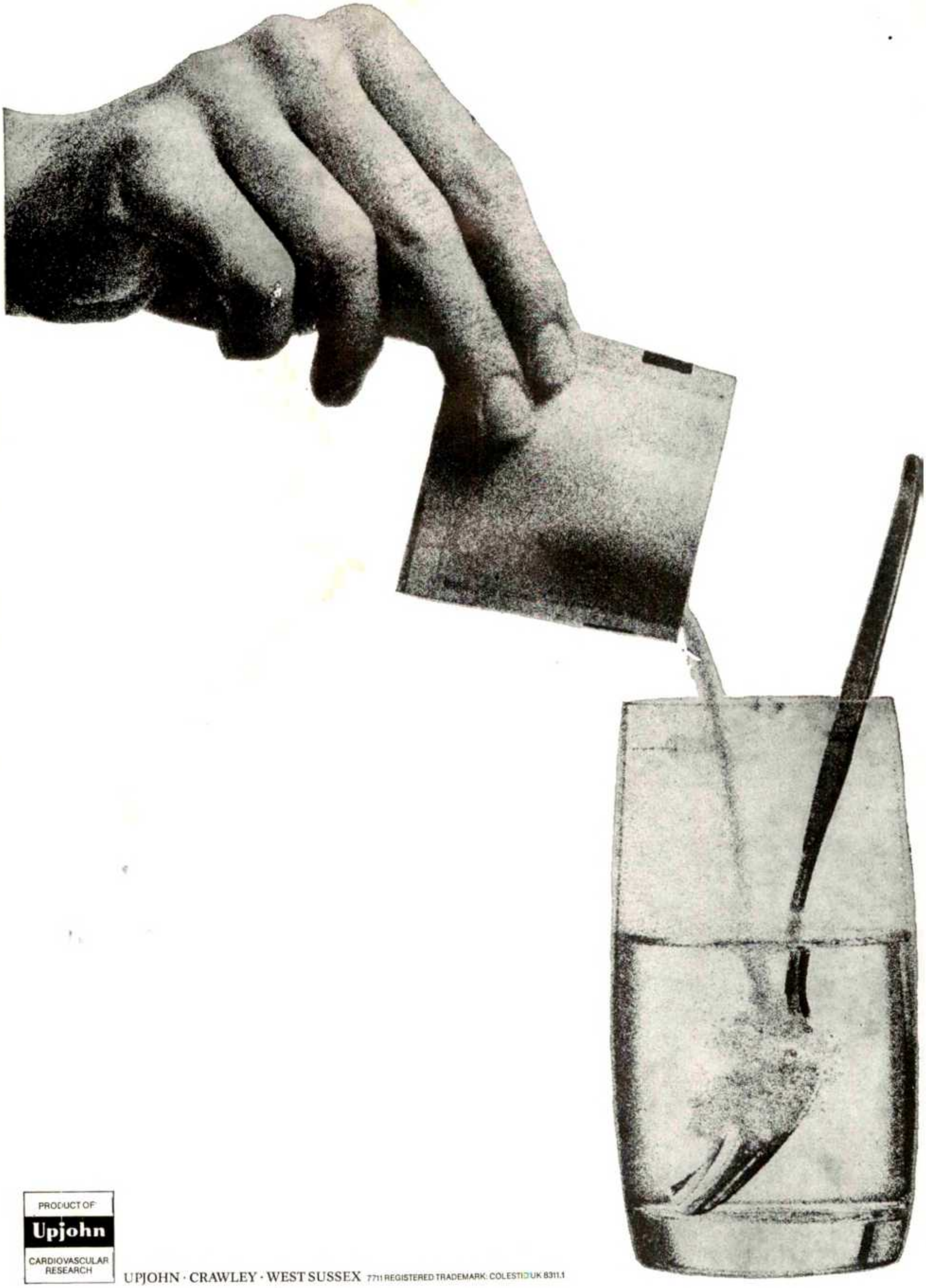

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References: 1. Med. J. Aust. (1973). *1*:1223.
2. JAMA (1972). 222:676.
3. New Zealand J. Med. (1972). *76*:12.

Prescribing Information

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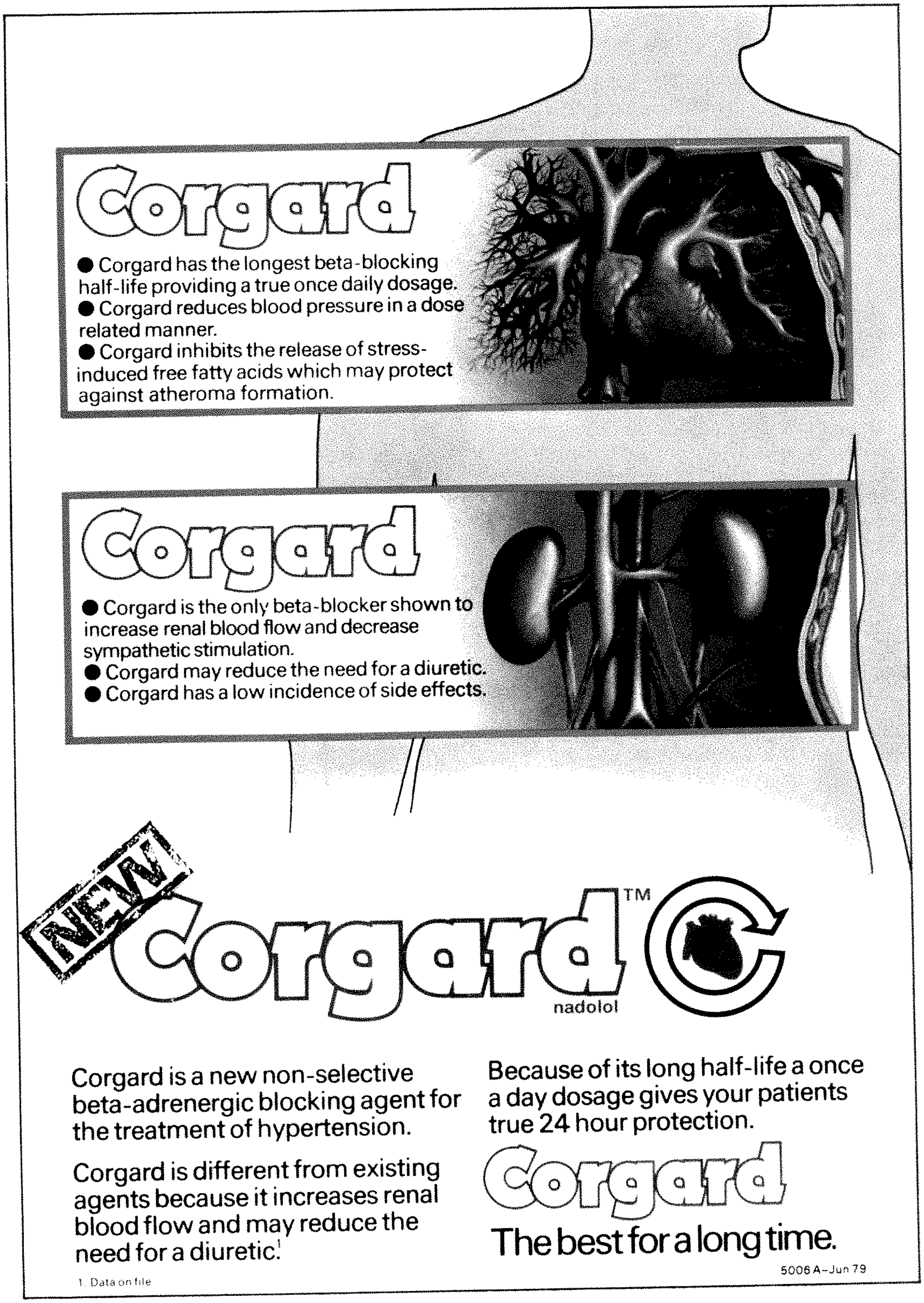

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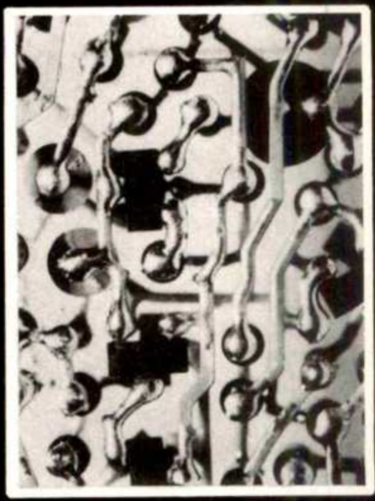

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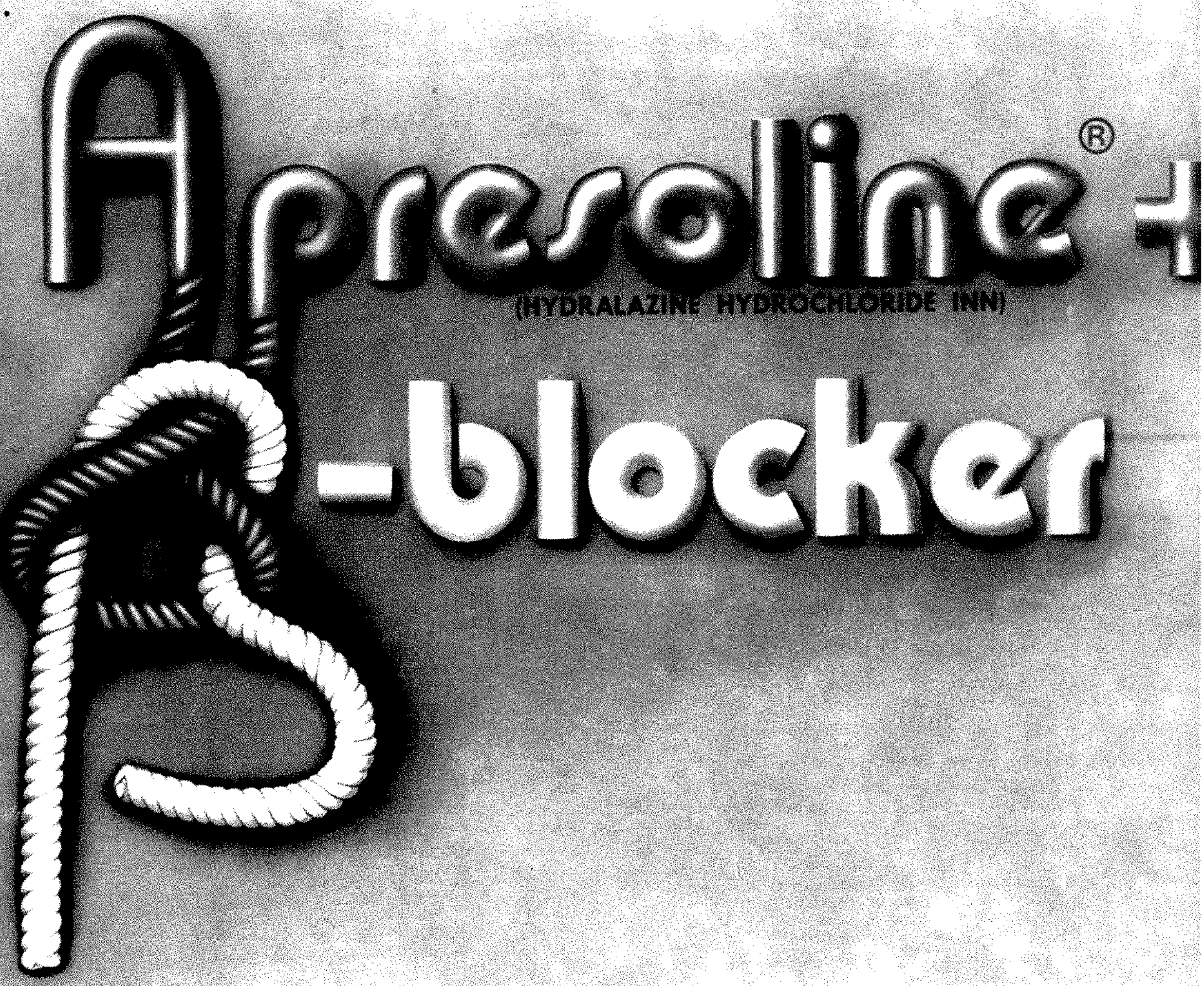

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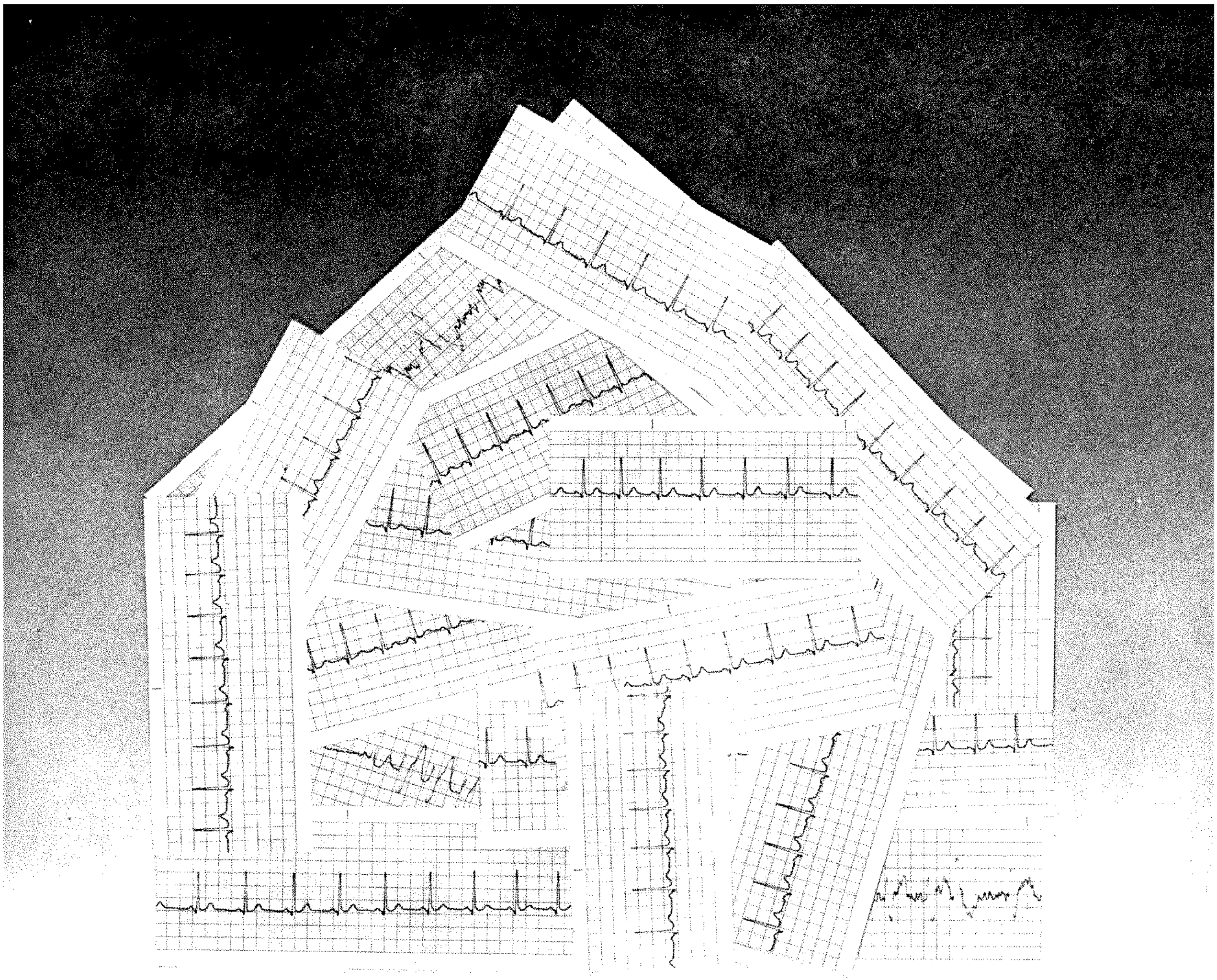

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British Heart Journal, 1979, **42**, 117-123

Low voltage electrical activity preceding right atrial depolarisation in man

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SUMMARY Electrical recordings were made in the high right atrium in 28 patients undergoing cardiac catheterisation and in 3 healthy volunteers. After filtering and amplification by 3 to 10 million times, the signals were passed through a signal averaging process in a digital computer. Of the 28 subjects who had technically satisfactory recordings, 23 showed low voltage electrical activity preceding the conventionally-recorded atrial depolarisation. The low voltage activity started 50 to 200 ms before the atrial deflection and was variable in shape. These early signals may be the result of activity in the region of the sinus node.

The rhythm of the healthy heart is controlled by the depolarisation of pacemaker cells in the sinus node. Animal sinus node tissue can be suspended in an organ bath and intracellular and extracellular recordings made from the pacemaker cells (West, 1955; Cramer *et al.*, 1977), but few convincing recordings have been made of the functioning sinus node in an intact mammalian heart. Some tracings have shown early activity in the high right atrium (Van der Kooi *et al.*, 1956; Ramlau, 1974; Théry *et al.*, 1976) but these early, high frequency signals are not clearly distinct from the earliest atrial activity (Masuda and Paes de Carvalho, 1975). No verified demonstrations have been published of the low frequency, low amplitude signals which would be expected to precede atrial activity in the high right atrium (Cramer *et al.*, 1977).

Hoffman and Cranefield (1960) predicted that sinus node activity should be recordable by small electrodes relatively far apart. The fundamental problem is that the very small signals may be smaller than the random background electrical activity ('noise'). In such circumstances an increase in amplification would not make the physiological signals any more discernible. We have attempted to record activity in the high right atrium in man using high amplification combined with signal averaging to reduce random background noise.

Method

Recordings were made with commercially-available hexapolar pacing wires using two electrodes 3·5 to 10 cm apart (Berkowitz-Castellanos, USCI). The pacing wire was inserted via a femoral, subclavian, or antecubital vein and positioned under fluoroscopic control with one electrode near the superior vena cava/right atrial junction and the other recording electrode in the superior vena cava or its tributaries.

The bipolar signals were amplified a thousand times with a low-noise, battery-powered amplifier (Ancom Limited, B9A-7D) and recorded on one channel of a four-channel tape recorder (Racal Thermionics, Store 4). This low-gain channel was used as a trigger for the signal averaging process (Fig. 1). After this initial amplification the same signals were filtered with a high pass cut-off of 3 to 10 Hz (Barr and Stroud EF3 filter, damped setting), amplified further by 10 to 100 times and recorded on another channel of the tape recorder. Lead I or II was recorded simultaneously.

On replay, in the computing laboratory, the high gain intra-atrial signals were filtered with a low pass cut-off of 150 Hz and a variable high pass cut-off within the range 10 to 20 Hz. At settings below 10 Hz the DC drift was too great to permit a high degree of amplification. With a cut-off above 20 Hz the signals of interest became less prominent. The high pass filtering was adjusted to remove as much as possible of the preceding T or U wave. The best

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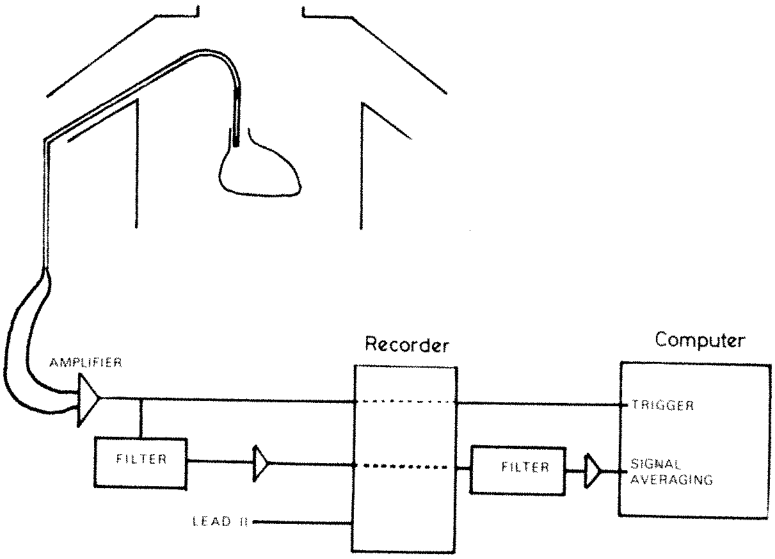

Fig. 1 *Block diagram of the recording and processing system.*

setting was usually between 10 and 14 Hz. The filtered, high-gain signals were amplified again to produce a total gain of 3 to 10 million.

For signal averaging, the cycles were added together in a general-purpose digital computer (Computer Technology Limited, Modular One). The analogue to digital converter accepted signal voltages in the range ±5V with a resolution of 5 mV per bit. The sampling rate was 3500 to 4000 Hz. The atrial depolarisation of the low gain channel was used to align the cycles correctly. Sixty to 600 cycles were averaged depending on the ease with which the noise was reduced, though at the high degree of amplification it was impossible to remove the random noise entirely. The results were plotted on a digital X-Y plotter (Calcomp 565). If necessary residual high frequency noise could be reduced by digital filtering before plotting.

The system of amplification and signal averaging was originally developed for the recording of external His bundle potentials. An earlier account (Vincent *et al.*, 1978) showed that a small artificial signal could be readily extracted from random noise by this signal-averaging system.

Acceptable triggering could be obtained using a simple threshold trigger on the upstroke of the low gain deflection, but results were more satisfactory with a pattern matching technique. For this technique the waveform of each atrial depolarisation was compared with a stored atrial signal. The beginning of the fresh signal was adjusted in time until the computer found the position for the best match with the stored signal. If the match was not close enough, that cycle was discarded. The beginning was then used as a reference point to add in the high gain signal to the averaging process.

As the exact position of the sinus node cannot be determined by fluoroscopy, simultaneous recordings were usually made with two pairs of electrodes on a single multipolar pacing wire. The active poles in the high right atrium were 1 cm apart.

Subjects

Recordings have been made on 3 healthy volunteers and 28 patients undergoing routine diagnostic cardiac catheterisation (Table). We have tended to select patients with slower heart rates, who have some separation between the electrical activity of the T wave and that of the following atrial depolarisation.

Results

Of the 31 subjects, 23 had recognisable electrical activity preceding the conventionally-recorded atrial activity in at least one recording. An example

Table *Diagnosis in 31 subjects*

Diagnosis	*No*
Sinus node disease	9
Other conducting system disease	8
Ischaemic heart disease	7
Normal volunteers	3
Miscellaneous	4

is shown in Fig. 2. Of the remaining 8 subjects, 5 had no clear interval between the end of the T or U wave and the start of atrial activity, 2 had unsatisfactory trigger signals, and the remaining 1 had distinct mains interference, which could not be removed by signal averaging.

The morphology of the early signal was variable. The commonest pattern (18 out of 23) showed an ill-defined onset with the early signal continuing into the atrial activity (Fig. 3 and 4). Four subjects showed little activity between the early signal and atrial depolarisation (Fig. 5). One subject with sinus node disease had a short, early signal with an abrupt onset and then a gap before the atrial deflection (Fig. 6).

The time from the onset of the early high gain signal to the start of the atrial activity in the low gain electrogram was in the region of 50 to 200 ms. In all cases the internal atrial activity was compared with the external P wave recorded in at least 2 (and usually 3) planes at right-angles to each other. The external signals never began before the internal activity. In this small series we found no systematic difference in the time from the onset of the early signal to the start of atrial activity between healthy volunteers and patients with sinus node disease. The longest interval (just under 200 ms) was in a 29-year-old man with syncope but no proven heart disease. The second longest (about 160 ms) was in a healthy 30-year-old volunteer.

The shape and, to a lesser extent, the time of onset of the early signal is dependent on the degree of high pass filtering used. It is, therefore, impossible to measure precisely the peak amplitude of the early signal but it may be in the range of 200–500 nanovolts.

The early signal was reproducible if a recording was reanalysed. In Fig. 7 and 8, the recordings of 2

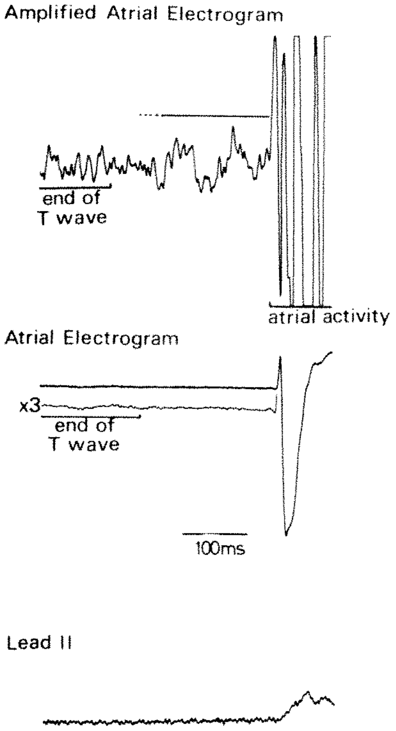

Fig. 2 *Simultaneous display of the highly-amplified atrial signals after the signal averaging process (top), the conventionally-recorded atrial electrogram (middle), and the electrocardiogram from the end of the T wave to the P wave (bottom). The horizontal line marks the approximate extent of the early signal. Part of the atrial electrogram is shown amplified 3 more times. The atrial activity in the highly-amplified recording is saturated. The filtering of the highly-amplified signal has reduced the duration of the T wave.*

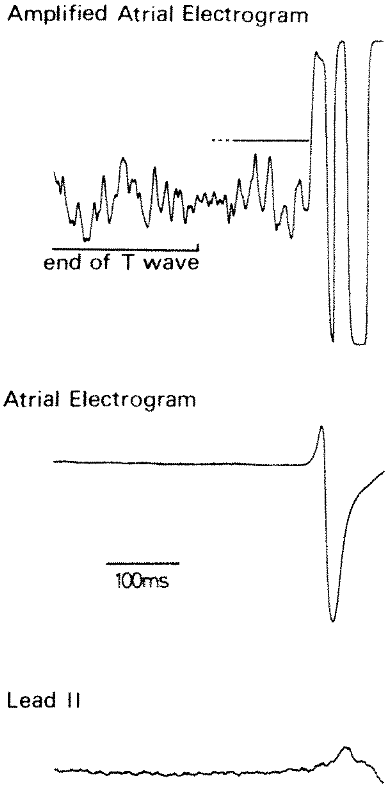

Fig. 3 *Another simultaneous display of the atrial signals after the averaging process, the atrial electrogram and the electrocardiogram. The horizontal line marks the approximate extent of the early signal.*

further subjects were reprocessed using non-identical cycles for the averaging technique. Some variations have occurred in the shapes of the early signals but the timings are unchanged.

Discussion

Sinus node disease is an important cause of morbidity and possible mortality, yet we do not know the aetiology in most cases (Shaw, 1976). Existing methods of diagnosis are unsatisfactory. If the electrocardiogram is normal, the most useful diagnostic procedure is 24-hour ambulatory monitoring (Lipski *et al.*, 1976). This technique reveals little or nothing of underlying mechanisms. The recovery time of the sinus node after overdrive suppression (Mandel *et al.*, 1971) and attempted calculations of the sinuatrial conduction time (Strauss *et al.*, 1973) have proved to be of little diagnostic value in most cases (Crook *et al.*, 1977). Any method which reveals direct information about the human sinus node would increase our understanding of sinus node disease and may ultimately have diagnostic implications.

We have demonstrated early signals preceding atrial depolarisation compatible with activity in, or close to, the sinus node. Their character and timing are similar to those predicted for the human sinus node signal, but there is no direct method of proving their origin. Previous recordings with epicardial electrodes placed on the sinus node of experimental animals have shown high frequency activity starting about 30 ms before the conventionally recorded atrial signal (Van der Kooi *et al.*, 1956; Ramlau, 1974; Théry *et al.*, 1976). But this

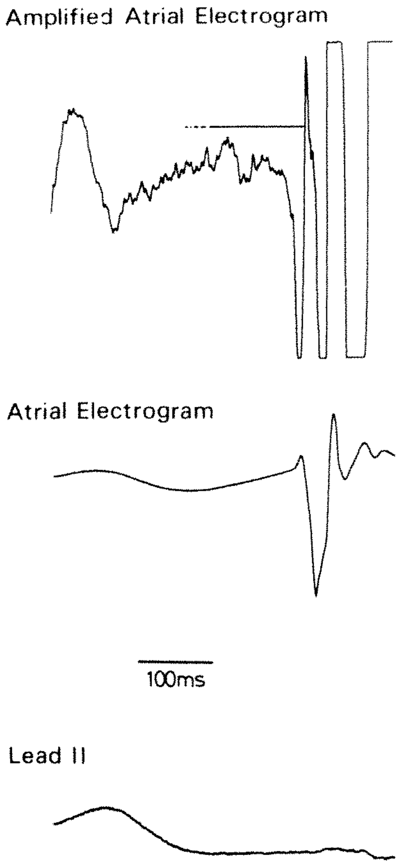

Fig. 4 *An example of the commonest pattern for the early signal. After an ill-defined onset the signal continues into the atrial activity.*

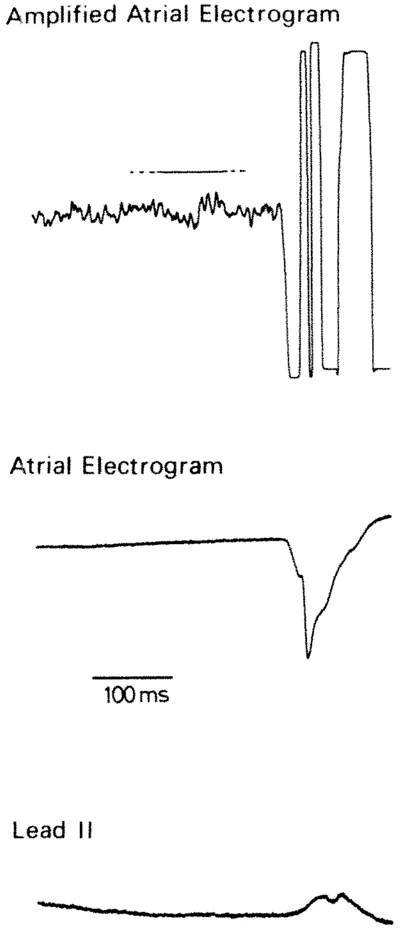

Fig. 5 *Another pattern for the early signal; the activity appears to diminish before the atrial depolarisation.*

high frequency activity is more likely to be produced by atrial rather than sinus node depolarisation (Masuda and Paes de Carvalho, 1975). Castillo-Fenoy *et al.* (1977) discovered early low frequency signals with a unipolar electrode applied to the dog sinus node. This presumed sinus node activity was recorded with surprising ease but clamps had been applied to the atria and the dog rendered anoxic to obtain the signals. Using signal averaging, Stopczyk *et al.* (1979) recorded early activity with intra-atrial electrodes in both dogs and humans, but these signals are not distinct from atrial activity or the end of ventricular repolarisation in the previous cycle. Similar studies in humans have been briefly reported, without illustrations or technical details, by other workers (Krongrad *et al.*, 1978; Tomita *et al.*, 1978). Cramer *et al.* (1977) have described extracellular potentials recorded from an isolated rabbit sinus node preparation. There were two potential changes. One was a slow continuous diastolic depolarisation; with our technique this would be removed by filtering. The other potential change was a faster depolarisation which began about 70 ms before the atrial activity. After filtering this second depolarisation would be similar in shape and timing to our early signals.

The time from the onset of our early signals to the earliest atrial activity was up to 200 ms. In the isolated rabbit atrial preparation the sinuatrial conduction time is 25 to 90 ms (Miller and Strauss, 1974; Yamaguchi and Mandel, 1975). In the slower human heart the sinuatrial conduction time is likely to be longer. In our experiments the apparent onset of atrial activity may have been influenced by the plane of the recording electrodes. However, any error must have been small because the internal atrial activity always began simultaneously with, or only just before, the external P wave recorded in at least two orthogonal planes.

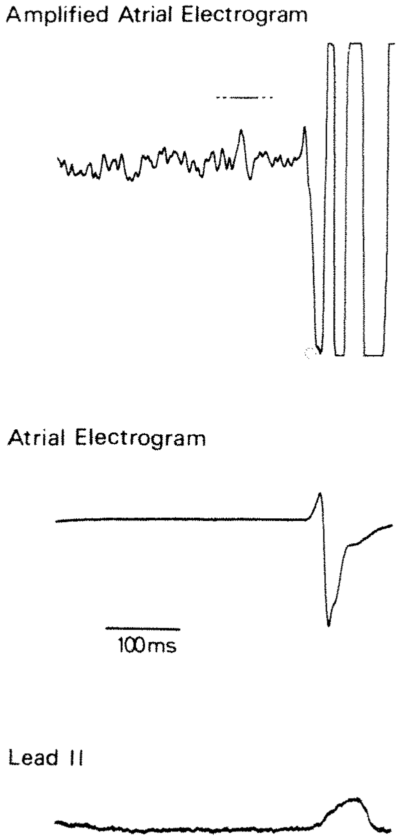

Fig. 6 *In this patient with sinus node disease the early signal has an abrupt onset with a gap before the atrial depolarisation.*

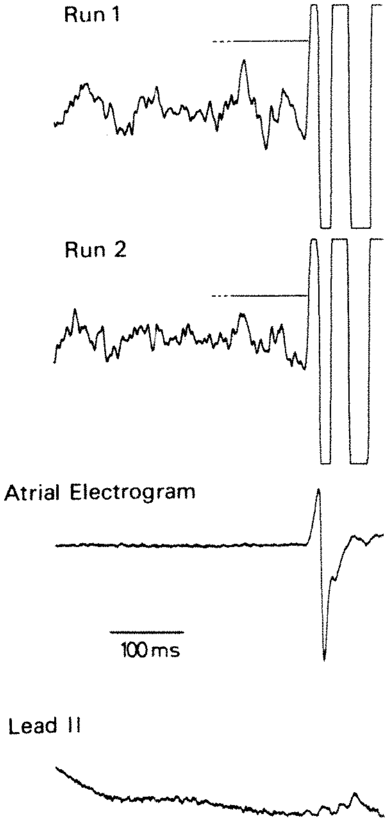

Fig. 7 *A comparison of the effects of averaging non-identical cycles from the same recording. The early signal varies in shape but not in timing.*

The early signal was reproducible in the same patient if another set of cycles was used for the averaging process. Unfortunately not all patients were able to lie still for sufficient time to record enough cycles. The results from 2 subjects who were able to remain quiet are shown in Fig. 7 and 8. The timing of the early signal has not changed appreciably but the shape has altered. Bonke *et al.* (1971) showed that the pacemaker site within the sinus node of rabbits shifted after premature atrial stimulation, and indirect evidence suggested that the point of impulse formation also varied during sinus rhythm in man (Cabanis *et al.,* 1978). Variations in shape of the early signal might be due to changes in the depolarisation wave within the sinus node.

We had to overcome two problems relating to the position of our electrodes. First, difficulty over the uncertain location of the sinus node was reduced by making simultaneous recordings from the active poles of two pairs of electrodes placed slightly differently in the upper right atrium; the better result was selected. Secondly, the effects of respiratory movement were reduced by the adoption of a pattern-matching technique for triggering. By accepting only a close match, signal averaging can be confined to signals sensed when the distal electrode is within a small area in the high right atrium. The pattern matching will also eliminate any ectopic beats from the averaging process, as ectopic or retrograde P waves will vary in shape from sinus ones.

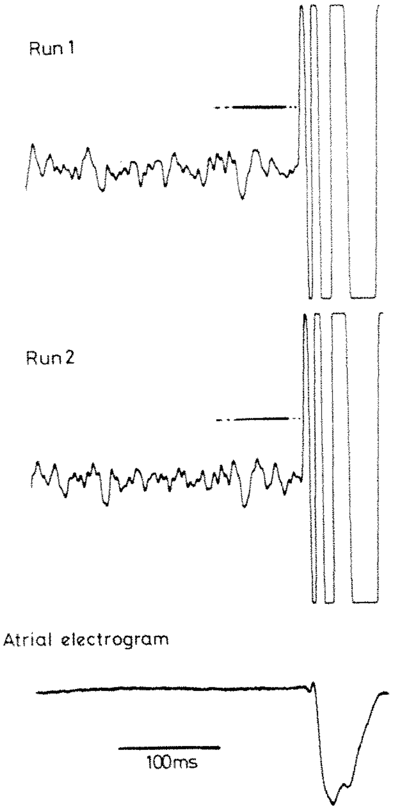

Fig. 8 *Another example of the effects of averaging non-identical cycles from the same recording. Again the early signal varies in shape but not in timing.*

Possible sources other than sinus node depolarisation should be considered for these early signals. The signals are likely to represent electrical activity within the heart; any signals which are not related to the cardiac cycle should be eliminated by the signal averaging. Previous recordings of early activity beginning 20 to 30 ms before the conventionally-recorded high right atrial activity have probably been produced by the onset of atrial depolarisation. Our early signals often begin sooner, over 100 ms before the conventionally-recorded atrial activity; it is unlikely that they are produced by the onset of atrial depolarisation. The end of the T or U wave of the previous cycle is a more plausible source for these early signals. A ventricular repolarisation signal may have frequency components similar to those of a sinus node signal, producing comparable waveforms on the recordings. However, any distant ventricular repolarisation would be continuous with the end of the T wave but not necessarily with the atrial depolarisation of the following cycle. When the heart rate was slow enough we observed a gap between the end of the T or U wave and our early signal. Moreover, the early signal continued into the atrial activity in 18 out of 23 cases.

The clinical implications of the recognition of these early signals is uncertain. We have not yet found any consistent difference in the shape or timing between patients with and without sinus node dysfunction, but the numbers are too small to draw firm conclusions. Furthermore, our experimental method may itself distort results especially if patients with sinus node dysfunction have variable conduction times from sinus node to atrium. Since our recording technique depends on the averaging of many cycles, good results can be obtained only when the time from sinus node depolarisation to atrial activation is fairly constant. Thus, subjects with potentially the most interesting results may produce the poorest recordings.

Despite inherent limitations in the present technique, the inevitable difficulty in the interpretation of very low voltage signals, and our uncertainty about clinical significance, we believe that studies of this type should be continued because sinus node activity is both important and ill-understood. Knowledge of sinus node function will be enhanced by reliable recordings of the electrical activity generated within it.

This work was carried out with the aid of grants from the British Heart Foundation. We are also indebted to Dr Oram and Dr Jewitt for their co-operation in this project.

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British Heart Journal, 1979, **42**, 124–127

Effect of nifedipine on atrioventricular conduction as compared with verapamil

Intracardiac electrophysiological study[1]

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SUMMARY Intravenous nifedipine, a powerful calcium antagonist, had no obvious effect on atrioventricular conduction when administered to 11 patients during routine intracardiac electrophysiological studies. Verapamil on the other hand showed potent antiarrhythmic properties, depressing atrioventricular nodal conduction. Nifedipine thus appears safe in patients with angina pectoris who have disorders of atrioventricular nodal conduction, and in those receiving beta-adrenergic blocking drugs.

There appear to be differential effects on the slow inward channels of cardiac cells with different 'calcium antagonists'.

Nifedipine, a powerful antagonist of transmembrane calcium influx in cardiac cells (Fleckenstein *et al.*, 1972), has been found to be useful in the treatment of angina pectoris (Camerini *et al.*, 1975). In vitro studies have suggested that nifedipine has effects on atrioventricular nodal tissue similar to those of the other calcium antagonists, as exemplified by verapamil (Taira and Narimatsu, 1975), though its action was more pronounced on coronary artery smooth muscle. However, work in the intact dog heart and observations of the surface electrocardiogram in patients receiving nifedipine have failed to show any significant depression of atrioventricular conduction (Ekelund and Oro, 1975; Taira *et al.*, 1975). If nifedipine does not depress intracardiac conduction, it may provide a useful alternative to the beta-blockers, particularly for patients with angina pectoris and pre-existing conduction abnormalities. The present study was undertaken to assess the effects of nifedipine administered intravenously during routine intracardiac electrophysiological studies and to compare these effects with those seen with verapamil during the same study.

Subjects and methods

Eleven patients, the details of whom are shown in Table 1, were studied during routine intracardiac electrophysiological investigations following the procedure previously described (Curry, 1975). In 5 patients paroxysmal reciprocating atrioventricular tachycardia was shown to be associated with an accessory pathway (Wolff-Parkinson-White syndrome) which was overt in 4 patients and concealed in the other. Two further patients who also had paroxysmal reciprocating atrioventricular tachycardia were shown to have re-entry circuits confined close to or within the atrioventricular node (cases 6 and 7). The remaining 4 patients had paroxysmal atrial fibrillation or flutter conducted to the

Table 1 *Age, sex, and clinical diagnosis in 11 patients*

Case	*Age*	*Sex*	*Diagnosis*
1	27	F	WPW 'B'
2	24	F	WPW 'A'
3	33	M	Concealed left accessory pathway
4	39	M	WPW 'A'
5	40	F	WPW 'A'
6	18	M	Intranodal reciprocating tachycardia
7	41	F	Intranodal reciprocating tachycardia
8	24	M	Paroxysmal atrial flutter (1:1 AV conduction)
9	56	M	Paroxysmal atrial flutter
10	52	M	Paroxysmal atrial fibrillation
11	62	M	Paroxysmal atrial fibrillation

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ventricles via the atrioventricular node.

In all patients nifedipine (7·5 μg/kg body weight) was injected intravenously over 3 minutes. The drug was drawn up under sodium light in a specially designed light-proof syringe. With one exception (case 6), the drug was given to the patients with paroxysmal reciprocating atrioventricular tachycardia during an established arrhythmia. Case 6 and the remaining 4 patients received the drug during continuous rapid atrial pacing. The method of atrial pacing was such that each paced atrial beat followed the previous QRS complex by a preset delay (60 to 80 ms) in a fashion that simulated re-entry tachycardia. Resting sinus cycle length and intracardiac conduction times (AH and HV intervals) were measured immediately before tachycardia was induced or atrial pacing started, and 5 minutes after the administration of nifedipine. During reciprocating tachycardia or atrial pacing the cycle length and the component regional conduction times (AH, HV, and VA intervals) were measured before and 3 minutes after nifedipine. Verapamil (0·15 mg/kg body weight) was administered to 10 of the 11 patients 45 minutes after nifedipine, as an intravenous bolus and under the same circumstances as nifedipine had been given. The results after verapamil were then compared with those obtained after nifedipine.

Results

Table 2 shows the effect of nifedipine on sinus rate and atrioventricular nodal and His-Purkinje conduction times 5 minutes after administration. In all but 1 patient (case 7) there was a shortening in sinus cycle length but in no patient was there a significant change in atrioventricular nodal conduction. When given during paroxysmal reciprocating atrioventricular tachycardia the arrhythmia was terminated in none (Table 3). There was no important change in cycle length or component conduction times except for 1 patient (case 4) in whom slowing occurred because of prolongation of atrioventricular nodal conduction. In this patient

Table 2 *Cycle length, atrioventricular nodal conduction time (AH interval), and His-Purkinje conduction time (HV interval) during sinus rhythm before and 5 minutes after administration of nifedipine 7·5 μg/kg i.v.**

Case	*Sinus cycle length(s)*		*AH*		*HV*	
	Before	*After*	*Before*	*After*	*Before*	*After*
1	550	430	80	75	0	0
2	710	540	75	80	20	20
3	740	650	100	100	40	40
4	590	495	85	85	20	20
5	590	515	90	85	0	0
6	660	540	75	75	35	35
7	600	610	110	110	35	35
8	710	640	120	120	40	40
9	575	525	50	50	50	50
10	650	560	75	75	40	40
11	980	840	65	65	35	35

* All measurements in this and subsequent tables are given in ms.

Table 3 *Change in cycle length (CL), atrioventricular nodal conduction time (AH), His-Purkinje conduction time (HV) and retrograde pathway conduction time to earliest atrial depolarisation (VA) before and 3 minutes after nifedipine in 6 patients with re-entry tachycardia*

Case	*CL*		*AH*		*HV*		*VA*	
	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1*	270	280	←—— antidromic tachycardia ——→					
2	295	295	145	145	35	35	90	90
3	450	430	205	185	50	50	160	160
4	280	330	100	150	45	45	80	80
5	255	255	110	110	30	30	90	90
6	290	285	115	120	35	35	140	130

* Case 1 had antidromic tachycardia and the relevant measurements could thus not be made.

Table 4 *Response, change in cycle length (CL), and atrioventricular nodal conduction time (AH) in 6 patients with re-entry tachycardia before and 3 minutes after nifedipine and 3 minutes after verapamil*

	Nifedipine				*Verapamil*			
	CL		*AH*		*CL*		*AH*	
	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	270	280			275	T		
2	295	295	145	145	300	T	155	T
3	450	430	205	185	420	T	175	T
4	280	330	100	150	280	T	100	T
5	255	255	110	110	280	T	135	T
6	290	285	115	120	295	T	120	T

T = termination of tachycardia.

Table 5 *Sinus cycle length and atrioventricular nodal conduction time (AH) before and 5 minutes after nifedipine and 5 minutes after verapamil*

Case	*Nifedipine*				*Verapamil*			
	Sinus cycle length(s)		*AH*		*Sinus cycle length(s)*		*AH*	
	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	550	430	80	75	530	490	80	90
2	710	540	75	80	740	650	75	80
3	740	650	100	100	800	740	100	135
4	590	495	85	85	630	550	85	95
5	590	515	90	85	520	505	90	100
6	660	540	75	75	620	590	75	140
7	600	610	110	110	680	610	110	155
8	710	640	120	120	630	530	120	125
9	575	525	50	50	Not given			
10	650	560	75	75	650	630	75	90
11	980	840	65	65	920	835	65	85

the tachycardia circuit showed considerable spontaneous variation and this change was within the range of previous and subsequent observations made while not receiving any medication. Similarly there was no effect in those patients in whom atrial pacing simulated re-entry tachycardia. Second degree atrioventricular block did not develop nor did the duration of atrioventricular conduction lengthen.

However, verapamil terminated proxysmal re-entry tachycardia in all 6 patients (Table 4); in the other 4 it lengthened atrioventricular nodal conduction time and refractoriness (Table 5), in keeping with its known antiarrhythmic properties (Krikler and Spurrell, 1974). Shortening of sinus cycle length after verapamil and nifedipine was of similar degree.

Discussion

The calcium-ion antagonist verapamil has a powerful depressant effect on conduction through the atrioventricular node (Cranefield *et al.*, 1974; Zipes and Fischer, 1974). Fleckenstein *et al.* (1972) showed in vitro that nifedipine was a considerably more potent calcium-ion antagonist than verapamil on a weight-for-weight basis. However, Taira and Narimatsu (1975), using an isolated dog atrioventricular node preparation, showed that the rate of blood flow through the atrioventricular nodal artery was about 10 times more sensitive to nifedipine than was the atrioventricular conduction time. This suggests that as coronary artery smooth muscle appeared to be far more susceptible to nifedipine than the cells that produce delay in atrioventricular nodal conduction, sufficient nifedipine to increase coronary blood flow might not slow atrioventricular nodal conduction. Furthermore, in the in situ paced hearts of open chest dogs nifedipine in a dose of 3 μg/kg intravenously facilitated atrioventricular nodal conduction if the heart had intact innervation, and also did not have a detrimental effect in the heart deprived of compensatory sympathetic drive by bilateral stellate ganglionectomy (Taira *et al.*, 1975). This facilitating effect of nifedipine was therefore ascribed to a sympathetic mechanism triggered by peripheral vasodilatation and hypotension. At a higher dose level (30 μg/kg) atrioventricular conduction was scarcely affected as long as the sympathetic nerve supply to the heart was intact, but after interruption of the sympathetic nerves both atrioventricular conduction time and the atrioventricular nodal functional refractory period were somewhat increased.

In clinical trials in man there have been no reports of adverse affects on atrioventricular conduction (Camerini *et al.*, 1975; Ekelund and Oro, 1975).

The present investigation was designed to assess the effect of intravenous nifedipine on atrioventricular conduction in patients undergoing routine intracardiac studies. Previous work (Curry *et al.*, 1978) has demonstrated the relation that exists between the electrophysiological properties of atrioventricular conduction and alteration in autonomic balance. The dose of nifedipine was 7·5 μg/kg body weight rather than 15 μg in order to avoid the increased sympathetic drive that accompanies the greater negative inotropic action of the larger dose (Lydtin *et al.*, 1976). Verapamil has been shown to exert a chronotropic action on sinus node activity by a baroreceptor-mediated increase in sympathetic tone (Breithardt *et al.*, 1978) and the similarity in the degree of acceleration of sinus node discharge after both drugs suggests that their peripheral effects are similar. Thus in this dose it is unlikely that an electrophysiological action on atrioventricular conduction is cancelled by an increase in sympathetic tone secondary to a fall in arterial pressure. Comparing the resting basic cycle length and the AH and HV intervals measured during sinus rhythm before and 5 minutes after nifedipine the only change was an acceleration of the heart rate (Table 2).

The administration of a nodal depressant drug during re-entrant atrioventricular tachycardia when the circulating impulse continually depolarises the nodal cells when they are in a state of partial recovery may exaggerate effects not apparent during sinus rhythm. However, tachycardia was never terminated by nifedipine, and in only 1 patient did atrioventricular nodal conduction time lengthen, even then no more than had been seen spontaneously. A similar lack of effect was found during atrial pacing. However, as previously recognised, verapamil exerted a potent antiarrhythmic action in all patients (Schamroth *et al.*, 1972; Krikler and Spurrell, 1974). The action of nifedipine given intravenously, as judged by haemodynamic changes in healthy volunteers and patients with ischaemic heart disease, does not appear to exceed 15 minutes (Lydtin *et al.*, 1975). Our results with verapamil are in keeping with other observations and do not suggest summation with a persisting action of nifedipine.

From the theoretical point of view, the fact that two slow channel inhibitors, verapamil and nifedipine, have such different effects on the atrioventricular node raises important considerations and perhaps warrants a reappraisal of the nature of the slow inward channel or channels. Our results show that verapamil exerts parallel haemodynamic effects and significant actions on the atrioventricular node while nifedipine exerts haemodynamic effects without depressing atrioventricular nodal function. Both agents have been shown to be potent inhibitors of the slow inward (calcium-dependent) channel and there appears to be either a qualitative or quantitative difference in the nature of the slow channel in smooth muscle and atrioventricular nodal cells.

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A 7-year analysis of haemorrhage in patients on long-term anticoagulant treatment

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SUMMARY Anticoagulant treatment reduces the risk of embolic and thrombotic complications in certain patients but haemorrhagic problems of the treatment have been less critically assessed. In this study 501 fully documented outpatients treated between 1970 and 1977, comprising 1199 patient-years of treatment, have been analysed in an attempt to clarify the iatrogenic risks of haemorrhage associated with oral anticoagulants.

Forty-one patients experienced 51 haemorrhages of sufficient severity to seek medical advice. The incidence was 8·2 per cent among patients and 4·3 per cent per treatment year. There were 24 occasions when the haemorrhage was potentially lethal and 2 patients died. In 23 of these 24 events, the prothrombin ratio at the time of haemorrhage was prolonged beyond the therapeutic range. In contrast, the prothrombin ratio was only known to be prolonged beyond the therapeutic range on 1 of the 27 occasions with less serious haemorrhages.

The risk of haemorrhage was unrelated to age and was greatest in those patients in whom the prothrombin ratio had proved difficult to control from the outset and in men with an aortic valve prosthesis. There was no cumulative risk in the first 3 years of treatment but a trend for increased risk between 4 and 7 years. It is in these groups with a high risk of bleeding that prothrombin control and patient education call for the closest attention.

The coumarin group of anticoagulants was developed by Link in the late 1930's (Link, 1943–1944) and their use in man first reported by Butt *et al.* in 1941. Since then they have been used to reduce the risk of embolic and thrombotic complications in certain patients. Over the years the spectrum of disease for which long-term oral anticoagulation is recommended has widened (*British Medical Journal*, 1972; Rogers and Sherry, 1976; Staffurth *et al.*, 1977). The therapeutic objective of achieving the lowest possible rate of thromboembolic complications must be weighed against the risk of haemorrhagic complications of therapy. The present study reviews the haemorrhagic complications of anticoagulation experienced in one anticoagulant clinic over a 7-year period.

Series and methods

In all, 509 outpatients attended between September 1970 and September 1977. Of these, 501 (242 men and 259 women) had case records available for examination—including 234 attending at the time the study was terminated—and form the basis of this analysis. Two hundred and forty-eight patients were interviewed personally. Four hundred and eighty patients (96%) were maintained on warfarin and 21 (4%) on dindevan. Prothrombin estimations (prothrombin ratio) were measured by the modified Quick test using British comparative thromboplastin (Dacie and Lewis, 1975). A case:control prothrombin ratio (PTR) between 1·8 and 2·6 to 1 was considered the desirable therapeutic range.

A significant haemorrhagic complication was defined as one in which a patient sought medical advice and received treatment, excepting minor bruising and minor epistaxes which are irregularly reported and therefore not included in this analysis. Significant haemorrhages were grouped into those episodes that were life-threatening (namely intracranial haemorrhage, haematemesis and melaena, and major retroperitoneal haemorrhage) and those which were not (see Table 2).

The probability of bleeding was calculated for each year-interval as the number of episodes of bleeding during each year-interval divided by the

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Table 1 *Indications for anticoagulation*

Indication	*Numbers*	
	Men (%)	*Women (%)*
Mitral valve disease/prosthesis	62 (12)	171 (34)
Aortic valve prosthesis	45 (9)	22 (4·5)
Double or triple valve prosthesis	2	5
Ischaemic heart disease	61 (12)	6
DVT/pulmonary embolism	40 (8)	31 (6)
Atrial fibrillation/arterial embolism	6	5
Coronary artery bypass grafts	11	2
Cerebrovascular disease	5	5
Peripheral vascular disease	3	5
Others	7	7
Total	242 (48)	259 (52)

total number of years of exposure to anticoagulants during each year.

Table 1 gives details of the indications for anticoagulation. Valvular heart disease and a prosthesis were the commonest indications for long-term treatment accounting for 61 per cent of the series. The mean duration of treatment per patient was 2·4 years (range 1 month to 7 years) and, in all, 1199 patient-years of treatment were assessed. The mean age (and standard deviation) of men was 54·3 (±9·7) years and of women 55·3 (±10·6) years. A mean of 12·5 prothrombin estimations was measured per annum for each patient.

Results

FREQUENCY OF HAEMORRHAGE

Fifty-one significant haemorrhagic complications occurred in 41 patients, 24 in 19 men and 27 in 22 women. The overall incidence of haemorrhagic complications was thus 8·2 per cent among patients (501 patients; 41 patients haemorrhage) and 4·3 per cent per patient-treatment-year (51 haemorrhages in 1199 years) or 1 per 23 treatment-years. Sites of haemorrhage are detailed in Table 2. The mean age of patients who bled was 47·8 (±11·5) years for men and 53·6 (±10·6) years for women, neither significantly different from the means for patients who did not bleed: 54·9 (±9·5) for men and 55·4 (±10·5) for women. Forty-nine weeks of in-patient hospital care were required for the management of these patients, the mean duration of stay being just under 9 days.

Table 2 *Sites of haemorrhage*

Site	*Number*
Life-threatening events	
Intracerebral haemorrhage	1
Subarachnoid haemorrhage	1
Haematemesis and melaena	12
Retroperitoneal haematoma	6
Other serious haemorrhages	
Perinephric haematoma	3
Haemarthrosis	1
Haematuria	6
Muscle/skin haematoma	5
Retinal haemorrhage	2
Epistaxis	9
Haemoptysis	1
Menorrhagia	3
Mixed	1
Total	51

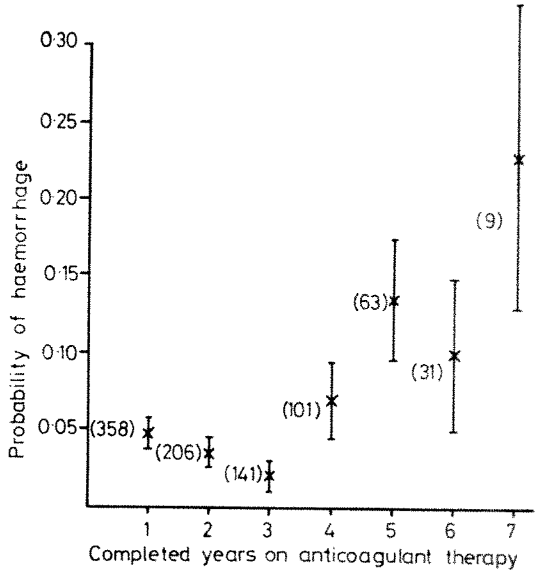

Fig. 1 *Probability of haemorrhage related to duration of therapy.*

The mean duration of anticoagulant treatment at the time of haemorrhage was 2·4 (±2·4) years for men and 2·9 (±2·1) years for women. To investigate whether anticoagulants had a durational effect, as far as the risk of haemorrhage was concerned, the probability of bleeding was calculated for each yearly interval for patients starting anticoagulants after 1970 (Fig. 1). There was no evidence of a cumulative effect over the first 3 years but some evidence of increasing risk between 4 and 7 years. Though the number of patient-years of treatment assessed for each year interval and shown in brackets decreases, the overall probability of haemorrhage in the first 3 years (0·04 ± 0·007) was less (P < 0·01) than the risk between 4 and 7 years (0·10 ± 0·025).

Two deaths were directly attributed to anticoagulants. One occurred in a 61-year-old woman (on warfarin for 10 months because of a mitral valve prosthesis) who became drowsy and later uncon-

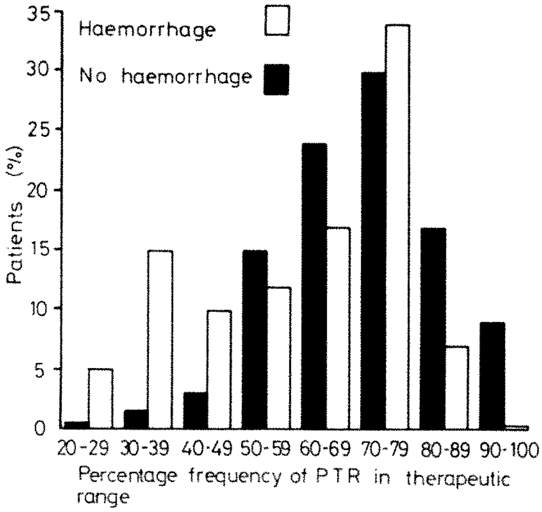

Fig. 2 *Anticoagulant control.*

scious 12 hours after hospital admission for observation of possible haematemesis. Prothrombin time on admission was > 120 seconds with control time of 12 seconds (PTR > 10:1) and her condition deteriorated despite reversal of anticoagulation with parenteral factor concentrate (factors II, VII, IX, X) and vitamin K_1 (10 mg). Death occurred 72 hours after admission, necropsy showing extensive subarachnoid haemorrhage with no identifiable vascular abnormality. The other death occurred in a 43-year-old man (on warfarin for 2 years because of an aortic valve prosthesis) who became suddenly unconscious. His prothrombin ratio on admission was 3·4:1. He was treated with parenteral vitamin K_1 (10 mg), but his condition deteriorated gradually, death occurring after 6 days from massive intracerebral haemorrhage with subarachnoid extension. Again, no vascular defect or occlusion was identified. In neither of these cases was the reason for the prolonged prothrombin ratio identified, ratios having been relatively stable in the weeks before admission. In both, platelet counts on admission were normal.

Table 3 *Prothrombin ratio at time of haemorrhage*

	Within therapeutic range (%)	*Beyond therapeutic range* (%)	*Unknown* (%)
Life threatening	1 (4)	23 (96)	0
Not life threatening	22 (81)	1 (4)	4 (15)
Total	23 (45)	24 (47)	4 (8)

ANTICOAGULANT CONTROL

The success of control of anticoagulant treatment was assessed for each patient as the number of prothrombin estimations within the therapeutic range expressed as a percentage of the total estimations performed on that patient. Fig. 2 shows the percentage frequency of prothrombin ratios within the therapeutic range for patients with and without haemorrhage plotted against the percentage of patients in each group. Control had been less good in those who bled, with higher percentages in the histograms to the left indicating poor control; 62·5 per cent of prothrombin estimations were within the therapeutic range in 'bleeders' compared with 70·1 per cent in 'non-bleeders', a highly significant difference ($P < 0.001$) in view of the large number of prothrombin ratios performed.

Table 3 shows the prothrombin ratios at the time of haemorrhage. Approximately half of all episodes occurred with the prothrombin ratio within the therapeutic range, but in 23 out of 24 episodes of life-threatening haemorrhage the prothrombin ratio was abnormally high. In contrast the prothrombin ratio was known to be prolonged beyond the therapeutic range in only 1 of the 27 occasions with less serious haemorrhage. Thus maintenance of the prothrombin ratio within the therapeutic range is almost always a protection against life-threatening haemorrhage but not less serious bleeding. Haemorrhage, however, did not always occur with an excessively prolonged prothrombin ratio. A prothrombin ratio greater than 3·4:1 was recorded overall in 2·5 per cent of patients who did not bleed.

In only 18 (35%) out of the 51 haemorrhagic episodes was a probable contributory factor for haemorrhage identified (Table 4). Drug induced haemorrhage was common, with aspirin or aspirin-containing compounds the most frequent offenders. An intrinsic gastrointestinal lesion (Crohn's disease, small bowel polyp, gastric carcinoma, and duodenal ulcer) was identified in 4 out of the 12 episodes of gastrointestinal bleeding.

Table 4 *Contributing factors in haemorrhage*

Factor	*Number of episodes*
Aspirin	4
Intrinsic GI lesion	4
Clerical error resulting in excess dosage	2
Phenylbutazone	2
Cotrimoxazole	1
Vancomycin	1
Ampicillin	1
Alcohol	1
Stopping barbiturate	1
Tetracycline	1
Total	18

Table 5 *Specific management of haemorrhage*

Treatment	*Number of episodes*
No change in anticoagulant dosage	16
Reduction in dosage	2
Anticoagulant temporarily stopped	13
Anticoagulant stopped + vitamin K_1	9
Anticoagulant stopped + factor concentrate	8
Anticoagulant stopped permanently	3
Blood transfusion	8
Operative intervention	8

Specific measures in the management of haemorrhage are indicated in Table 5. Laparotomy was undertaken on 3 occasions for uncontrolled gastrointestinal bleeding after reversal of anticoagulant effect, and a lesion was identified at operation on 1 occasion. Nephrectomy was required twice for perinephric bleeding and cystoscopy on 3 occasions for haematuria.

HAEMORRHAGE AND AORTIC VALVE PROSTHESIS

Of the 19 men who bled, 10 (53%) had aortic valve prostheses compared with 223 non-bleeding men of whom 35 (16%) had such prostheses ($P < 0{\cdot}01$). The corresponding female figures were 22 bleeders with 3 (14%) aortic valve prostheses and 237 non-bleeders with 19 prostheses (12·5%) (NS). The reason for the increased risk of haemorrhage in men is unclear and has not been previously reported.

Discussion

During the 1950's the use of oral anticoagulants was more controversial than it is today (Gilchrist and Tulloch, 1956), but areas of controversy remain. Haemorrhage accounts for the majority of complications of treatment, and knowledge of its frequency is an important element in deciding on anticoagulant usage. Strict comparison between the results in different series is made difficult by differences in the technique of measuring prothrombin time and in the reporting of results, variation in the accepted therapeutic range between different centres (Lam-Po-Tang and Poller, 1975), and the need to take account of the duration of treatment. The problem is further compounded by different criteria adopted for definition of haemorrhage and the fact that the numbers of patients experiencing haemorrhage are not necessarily the same as the numbers of episodes of haemorrhage, since one patient may have more than one episode.

The incidence of haemorrhage has varied widely in reported series, in all of which the number of patient-years of treatment studied has been less than in the current series. Peyman in 1958 refers to studies where the incidence of haemorrhagic complications varied from a few to over 40 per cent. Pollard *et al.* in 1962 reported a high incidence of haemorrhage (47 out of 139 patients, or 34%); 69 per cent of the bleeding episodes occurred with the prothrombin time in the therapeutic range, but 13 out of 14 episodes of major haemorrhage were associated with a prolonged prothrombin time. More recently, Husted and Andreasen (1976) found bleeding in 34 of 114 cases (30%), 69 per cent of these showing a prothrombin time in the therapeutic range at the time of bleeding. Coon and Willis (1974) found bleeding in 6·8 per cent of 3862 'courses' of oral and parenteral anticoagulant therapy. Among 217 patients maintained on oral anticoagulant therapy, Fleming and Bailey (1971) reported 1 death, 16 (7·4%) major, and 18 (8·3%) minor episodes of bleeding. Their survey covered a total of 649 patient-treatment-years giving a complication rate of 5·2 per cent per treatment-year. The series reported here shows an incidence of haemorrhage among the 501 patients of 8·2 per cent related to a mean duration of treatment of 2·4 years while the rate of haemorrhagic episodes calculated per treatment-year was 4·3 per cent. The results reported here support the view expressed by Pollard *et al.* that maintenance of the prothrombin ratio within the therapeutic range does not necessarily prevent haemorrhage, but protects against life-threatening haemorrhage.

It seems unlikely that either of the deaths from intracranial haemorrhage could have been prevented. Fatal intracranial haemorrhage is rare (Coon and Willis, 1974), but is likely to be underestimated because of the difficulty in some instances of distinguishing clinically between cerebral embolism and cerebral haemorrhage. This emphasises the importance of a necropsy in all patients whose deaths occurred while they were on anticoagulants.

It is somewhat surprising that a clear contributory factor was identified in only 18 out of the 51 bleeding episodes. Aspirin related bleeding may have occurred more frequently than indicated because of its presence in a wide variety of commercial preparations. The rarity of antibiotic induced haemorrhage is interesting in view of the frequency of the prescription of these drugs in the population studied.

The lack of significant correlation between age and risk of bleeding differs from previous reports (Pollard *et al.*, 1962; Coon and Willis, 1974). Age alters the clinical response to anticoagulants (O'Reilly and Aggeler, 1970; Hewick *et al.*, 1975;

Husted and Andreasen, 1977), either through a reduction in plasma protein binding or depression of hepatic synthesis of clotting factors. However, provided patient compliance and understanding are good and appropriate adjustments of dosage are made, age need not constitute a hazard in treatment and should not by itself be regarded as a contra-indication to use.

Patients with valve prostheses consequent on rheumatic heart disease accounted for most of the group reported here. Such patients are at risk from periodic, sometimes prolonged, hepatic congestion which can profoundly impair drug catabolism and delay clotting factor synthesis (Hewick *et al.*, 1975). This may in part explain the different responses to oral anticoagulants at different times in the same patient.

The use of factor concentrate (factors II, VII, IX, X) in the management of haemorrhage from excess oral anticoagulation has advantages over vitamin K_1 (Taberner *et al.*, 1976) and has been a significant advance in reducing the mortality and morbidity of these drugs. Factor concentrate has been freely available in this region for the past 3 or 4 years and allows immediate controlled reversal of anticoagulation without prejudicing later reintroduction of anticoagulant drugs.

Three groups of patients have been identified in whom the risk of haemorrhage is greatest. The first group are those patients in whom the prothrombin ratio has proved difficult to control from the outset; the second group are men with aortic valve prostheses, and the third are patients after 3 years on long-term treatment. Anticoagulants do carry a significant risk of haemorrhage and their long-term use in any patient should be based on firm evidence of efficacy. It is in the 3 groups mentioned that prothrombin control and patient education call for the closest attention, with frequent assessment of dosage. Patients with stable prothrombin ratios have a low risk of major bleeding and may be assessed less frequently.

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Recurrence of myocardial infarction in an exercising population[1]

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SUMMARY The Ontario Multi-Centre Exercise-Heart Trial is making a prospective study of 751 male subjects following well-documented episodes of myocardial infarction. Comparison is here made between the 50 participants who sustained a recurrence of their myocardial infarction, and the 701 participants who did not. Reinfarction was a little more likely with a history of multiple previous infarctions, but was unrelated to such indicators of infarct severity as symptoms, electrocardiographic abnormalities, enzyme changes, cardiac arrest, arrhythmia, or minimum systolic blood pressure. Features noted on admission to the trial, which may have an adverse effect, include smoking history and related symptoms, residual disability, shortness of breath, and angina of effort. The main physiological warning sign was a low and decreasing cardiac output at a submaximal work load, with a compensatory widening of arteriovenous oxygen difference. With the possible exception of exercise non-compliance, none of the adverse findings is sufficiently consistent to be of value when advising individual patients.

Previous work (Shephard, 1979; Kavanagh and Kennedy, 1977) has indicated that traditional 'coronary risk factors' are modified after infarction, particularly if the patients concerned are participating in a vigorous, exercise-centred rehabilitation programme. Given a recurrence rate of up to 4 per cent per annum, it would increase the safety of rehabilitation programmes if those patients with an above average risk of a further coronary event could be identified. Unfortunately, there are at present few clues to the detection of such individuals (Shephard *et al.*, 1977; Shephard, 1979).

The Ontario Multi-Centre Exercise-Heart Trial (Rechnitzer *et al.*, 1975) has now followed 50 of its 751 patients to the point of reinfarction. The opportunity has now been taken to compare these patients with the other participants in terms of (i) characteristics of the primary episode, (ii) clinical features on admission to the trial, and (iii) physiological responses to exercise, followed prospectively.

Subjects and methods

The subjects were 751 patients enrolled in the Ontario Multi-Centre Exercise-Heart Trial[1]; this has as its prime purpose a comparison of vigorous endurance activity and light recreation in the treatment of 'post-coronary' patients. Initial selection criteria are detailed elsewhere (Rechnitzer *et al.*, 1975). In brief, patients 54 years or younger were admitted to the trial 3 to 12 months after a myocardial infarct proven by 2 of 3 criteria (typical history of chest discomfort, serial electrocardiographic abnormalities typical of a transmural or subendocardial infarction, and typical changes in serum levels of AST (SGOT) or CK). Specific grounds for exclusion from the study included heart failure, a diastolic pressure in excess of 110 mmHg, insulin-dependent diabetes, orthopaedic disabilities, and gross abnormalities of pulmonary function ($FEV_{1.0}/VC < 60\%$).

After recruitment and clinical examination, subjects were allocated in a stratified random fashion to either a high intensity endurance exercise regimen or a low intensity recreational exercise programme. Both groups attended the rehabilitation centres regularly, and referring physicians received standardised advice on diet and other aspects of 'lifestyle'.

Detailed physiological tests were carried out on admission, and at 6 months, 12 months, 2, 3, and 4 years after recruitment. When patients were receiving propranolol or similar medications, the responsible clinician was approached one week before exercise testing, and asked to agree to a graded withdrawal of the drug. In a few subjects, this was deemed inadvisable, and at various points in the study it was necessary to test 5 to 7 patients who

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[1] Ontario Multi-Centre Exercise-Heart Trial.

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were receiving treatment by beta-blocking drugs. The influence of such treatment on the test results is discussed where appropriate.

CLINICAL DATA

All clinical information relating to the primary episode and the condition on admission to the trial was recorded in a predetermined objective format.

PHYSIOLOGICAL TESTS

Lung volumes were determined by standard Stead-Wells spirometers with lightweight bells.

Exercise testing was carried out on electrically-braked bicycle ergometers, using a three-load progressive submaximal procedure; 6 to 8 minutes were allowed per test stage, the final loading being adjusted to a heart rate corresponding to 75 per cent of maximum oxygen intake.

Oxygen consumption, carbon dioxide output, and ventilatory measurements were made by a standard open-circuit technique (Shephard, 1977). Cardiac output and related measurements were obtained by the rebreathing technique of Jones and his associates (1975). Particular attention was directed to the standardisation of techniques between co-operating laboratories (Jones and Kane, 1979).

Results

(1) CHARACTERISTICS OF THE PRIMARY EPISODE[1]

(a) *Chest pain*

In those remaining free from recurrence during the prospective study, the primary episode had given rise to no chest pain in 11 subjects (1·6%), slight pain in 92 (13·3%), and severe pain in 587 (85·1%); no data were available for 11 subjects. In the 50 patients who developed a further infarction, symptoms were no more severe, 7 cases showing slight pain (14%) and 43 (86%) severe pain.

(b) *Diagnostic electrocardiographic abnormalities*

Six subjects without a recurrence (0·9%) showed no diagnostic electrocardiographic abnormalities, and in a further 56 (8·1%) changes were rated as 'borderline', leaving 627 (91·0%) with clearly diagnostic electrocardiograms and 12 subjects where electrocardiographic reports were not available. The proportion of cases with clear-cut electrocardiographic abnormalities (46/49, 93·9%) was insignificantly greater in those sustaining a recurrence.

(c) *Serum enzyme changes*

Enzyme data were available for 713 subjects (666 without, and 47 with a recurrence of infarction). Of those remaining free from infarction, enzyme changes were absent in 33 (5·0%), marginal in 55 (8·3%), and diagnostic in 578 (86·7%). Of those patients who had a recurrence, 5 patients (10·6%) showed no change, 1 (2·1%) a marginal change, and 41 (87·3%) a diagnostic increase.

(d) *Cardiac arrest*

One episode of cardiac arrest occurred in 36 of 689 patients (5·2%) free from recurrence, and 2 episodes or more occurred in 8 cases (1·2%). Such events were not significantly less frequent in those sustaining a recurrence (1 case, 2%, with a single episode of cardiac arrest).

(e) *Arrhythmia*

Occasional arrhythmia was observed in 196 of 683 subjects (28·7%) without recurrence, and frequent arrhythmia was encountered in 68 (10·0%). The occurrence of arrhythmia was very similar in those with a recurrence (15/49, 30·6%, had occasional arrhythmia and 5/49, 10·2%, frequent arrhythmia).

(f) *Minimum systolic blood pressure*

The mean minimum recorded systolic blood pressure was almost identical in those without (106·6 ± 2·98 mmHg) and those with a recurrence (105·8 ± 1·97 mmHg).

(g) *Number of previous infarctions*

Details of previous history were available for 689 patients without a recurrence during the period of observation: 52 (7·5%) had had 1 earlier infarct, 2 (0·3%) 2 previous infarcts, and 2 (0·3%) 3 previous infarcts. Proportions were slightly ($0·1 > P > 0·05$) higher for those developing a recurrence during the study (5 cases, 10%, with 1 infarct, 1 case, 2%, with 2 infarcts, and 1 case, 2%, with 3 infarcts).

(2) CLINICAL FEATURES ON ADMISSION TO THE TRIAL[1]

(a) *Smoking history and cardiorespiratory diseases*

The proportion of continuing smokers among those free from recurrence (248/696, 35·6%) was much as in other studies of post-coronary patients (Coronary Drug Project Research Group, 1975; Kavanagh *et al.*, 1977); 386 (55·4%) of 696 had stopped smoking, and 62 (8·9%) had never smoked. Proportions of smokers were marginally higher ($0·1 > P > 0·05$) among those sustaining a recurrence: 24 (48%) of 50 continued to smoke, and 24 (48%) were previous smokers.

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[1] Data were not always available for all 701 cases without a recurrence or for all 50 cases with a recurrence.

Classifying subjects by the reported depth of smoke inhalation, 62 of 692 (8·9%) of those without recurrence noted 'slight' inhalation, 233 (33·7%) 'moderate' inhalation, and 295 (42·6%) 'heavy' inhalation. Of those with a recurrence, there was a slight suggestion (0·2 > P > 0·1) that more were reporting 'heavy' inhalation (27/50, 54%), but proportions with 'moderate' (15/50, 30%) and 'slight' inhalation (4/50, 8%) were much as in those without recurrence.

Probably because of its association with smoking, there was also a slight indication (0·2 > P > 0·1) that prognosis was affected by an initial history of wheezing. Of 698 without a recurrence, 143 (20·5%) experienced occasional wheezing, and 18 (2·6%) were wheezing most of the time. Of 49 with a recurrence, 15 (30%) were wheezing most of the time.

Other chest conditions also had a slight relation to prognosis. Haemoptysis was recorded in 3 patients (6%) with a recurrence, compared with 15 cases (2·2%) in those free from recurrence (0·1 > P > 0·05). Phlegm was produced on most days by 8 (16%) of those with a recurrence, compared with 65 (9·3%) of the remainder (699); winter sputum and/or sputum for 3 months of the year was likewise recorded in 5 subjects (10%), compared with 48 (6·9%). The combined χ^2 (2 degrees of freedom) for sputum production was 3·34 (0·2 > P > 0·1).

(b) *Activity and employment history*

When first seen, a small majority of those who remained free from recurrence were less active than before their infarction (354/699, 50·6%). In those with a recurrence (34/50, 68%) the proportion inactive was significantly greater (0·02 > P > 0·01). The reported daily walking distance was allocated to 1 of 3 categories (< 1 mile, 76/697, 10·9%; 1 to 3 miles, 162/697, 23·2%; > 3 miles 459, 65·8%); there was a statistically insignificant suggestion that those with a recurrence favoured the two lower categories of exercise (< 1 mile 6/50, 12·0%; 1 to 3 miles, 16/50, 32·0%; > 3 miles/day, 28/50, 56·0%).

The proportions continuing with their old job were rather similar in those without (515/699, 73·7%) and those with (34/50, 68·0%) a recurrence, but there was a slight but statistically insignificant suggestion of a change to part-time work in those with a recurrence (5/50, 10·0% compared with 51/699, 7·3%). Further, more of those sustaining a recurrence were engaged in light work (30/50, 60%) than were those who remained free from recurrence (333/699, 47·6%) (0·1 > P > 0·05).

The group with recurrent infarction contained more subjects engaged in commerce and financial activities than the group with no recurrence (38·0% vs. 17·7%, P < 0·001), and fewer subjects engaged in professional and managerial work (16·0% vs. 47·2%, P < 0·001). Work involving a combination of walking and lifting was also possibly a little more common (0·2 > P > 0·1) in those sustaining a recurrence (9/50 18%) than in those who did not (77/701, 11·5%).

Shortness of breath on exertion was reported by 41 (82%) of 50 with a recurrence, but by only 282 (39·4%) of 698 free from reinfarction, a highly significant difference (P < 0·001). Differences were apparent at all levels of dyspnoea (during brisk level walking, 28% versus 11%, when ascending a slight gradient, 38% versus 22%, and more severe grades of dyspnoea, 16% versus 6·7%).

(c) *Effort angina*

The proportion of the sample free from angina was similar in those who developed a recurrence (24/50, 48%) and in those who did not (356/697, 51·1%). However, those without a recurrence had fewer attacks during exercise, and more attacks at other times. Respective figures were for uphill or brisk walking 110 of 697 (15·8%) vs. 14 of 50 (28·0%), for level walking (sum of two categories) 62/697 (8·9%) vs. 5/50 (10·0%), and for other types of angina 169/697 (24·2%) vs. 7/50 (14·0%). The combined χ^2 for 3 degrees of freedom was 6·42 (0·1 > P > 0·05).

Neither the site of reference nor the duration of angina was helpful in distinguishing those who developed a recurrence of their infarction. Glyceryl trinitrate was taken by 11 (22·0%) of 50 with a recurrence, compared with 125 (18·8%) of 694 without. Calf pain on ordinary level walking was reported by 3 (6·0%) of 50 who had a recurrence, compared with 38 (5·4%) of 699 without recurrence.

(d) *Personality*

The proportions classed as having a type A personality (35/50, 70·0%, vs. 492/701, 70·2%) were very similar in those with and those without a recurrent infarction.

(3) PHYSIOLOGICAL RESPONSES

(a) *Lung volumes*

Initial spirometric values were not significantly less good in those sustaining a recurrence ($FEV_{1.0}$ 3·19 ± 0·18 vs. 3·35 ± 0·68 l BTPS, FVC 4·19 ± 0·81 vs. 4·26 ± 0·76 l BTPS).

(b) *Respiratory response to exercise*

For the purpose of comparing those with and without a recurrence of infarction, all data were stan-

Table 1 *Respiratory variables on entry to the study (E) and at 6, 12, 24, 36, and 48 months: comparison between data for patients with and without a recurrence of their infarction*

Variable and time (m)	*No recurrence*	*Recurrence*
V_D/V_T		
E	0·22 ± 0·07	0·23 ± 0·05
6	0·21 ± 0·08	0·18 ± 0·06
12	0·21 ± 0·07	0·27 ± 0·10*
24	0·22 ± 0·07	0·28 ± 0·06*
36	0·21 ± 0·06	—
48	0·26 ± 0·07	—
P_{aO_2} (mmHg)		
E	87·4 ± 8·2	89·9 ± 8·3
6	88·1 ± 7·7	86·6 ± 8·3
12	87·7 ± 8·3	85·3 ± 4·7
24	87·3 ± 8·2	75·7 ± 7·9*
36	89·4 ± 7·3	—
48	85·2 ± 6·7	—
$P_{(A-a)O_2}$ (mmHg)		
E	21·8 ± 10·1	18·6 ± 9·7
6	20·3 ± 7·7	21·3 ± 10·1
12	21·6 ± 8·0	22·2 ± 10·2
24	20·1 ± 8·3	26·6 ± 6·8
36	17·7 ± 7·8	—
48	20·8 ± 5·9	—
Gas exchange ratio (R)		
E	0·94 ± 0·11	0·90 ± 0·11*
6	0·94 ± 0·10	0·89 ± 0·09*
12	0·95 ± 0·09	0·89 ± 0·08*
24	0·93 ± 0·10	0·89 ± 0·09
36	0·94 ± 0·12	—
48	0·92 ± 0·09	—

Note: Data expressed as mean ± SD, standardised to a $\dot{V}O_2$ of 1·25 l/min STPD. Details of sample size and differences between patients receiving high and low intensity exercise (all statistically insignificant) are available on request.

Significance of difference between patients with and without a recurrence of infarction: *P < 0·05.

Table 2 *Cardiovascular variables on entry to the study (E) and at 6, 12, 24, 36, and 48 months: comparison between data for patients with and without a recurrence of their infarction*

Variable and time (m)	*No recurrence*	*Recurrence*
Cardiac output (l/min)		
E	11·2 ± 2·3	10·8 ± 1·9
6	11·0 ± 1·9	10·2 ± 2·1*
12	11·1 ± 1·8	9·9 ± 2·0*
24	11·1 ± 1·6	10·3 ± 2·1
36	11·3 ± 2·6	
48	10·2 ± 1·1	
Stroke volume (ml)		
E	95·0 ± 24·4	91·9 ± 24·0
6	95·5 ± 21·5	89·4 ± 22·8
12	96·3 ± 20·9	87·5 ± 22·5
24	96·9 ± 16·6	97·0 ± 19·1
36	100·1 ± 19·5	
48	92·0 ± 22·3	
Arteriovenous oxygen difference (ml/l)		
E	116 ± 23	119 ± 22
6	117 ± 20	127 ± 31*
12	115 ± 19	131 ± 29**
24	115 ± 19	121 ± 14
36	114 ± 20	
48	125 ± 13	
Heart rate (bpm)		
E	119·3 ± 16·9	118·9 ± 15·0
6	115·8 ± 15·9	115·3 ± 13·0
12	116·5 ± 16·6	113·7 ± 13·7
24	114·6 ± 15·2	108·0 ± 16·4
36	112·8 ± 18·0	
48	112·1 ± 17·2	

Note: Data expressed as mean ± SD, standardised to a $\dot{V}O_2$ of 1·25 l/min STPD. Details of sample size and differences between patients receiving high and low intensity exercise (all statistically insignificant) are available on request.

Significance of difference between patients with and without a recurrence of infarction: *P < 0·05 **P < 0·01.

dardised by interpolation to a common oxygen consumption of 1·25 l per min STPD.

The majority of the respiratory measurements (respiratory minute volume, breathing rate, tidal volume, and alveolar ventilation) showed no differences between the groups. However, there were slight indications of a high dead space/tidal volume ratio, a low arterial oxygen pressure, an increased alveolar-arterial oxygen pressure gradient, and a low gas exchange ratio in those sustaining a reinfarction. With the exception of the low respiratory gas exchange ratio, these differences became more obvious as the period of observation was extended and the date of reinfarction was approached (Table 1).

(c) *Cardiac response to exercise*

The initial exercise cardiac output tended to be low in those patients who later had a recurrence of their infarction (Table 2). This difference became statistically significant at 1 year. The available data suggest that a decrease of stroke volume rather than heart rate was responsible. There were compensatory increases of arteriovenous oxygen difference, significant at 6 and 12 months of observation.

Exclusion of the few patients who were receiving beta-blocking drugs at the time of testing made little difference to the overall results. Thus, the mean heart rate of the patients without a recurrence dropped from 119·8 ± 15·7 (on entry) to 113·6 ± 14·3 (at 2 years) in the high intensity endurance group, and from 119·4 ± 17·6 (on entry) to 116·3 ± 15·9 (at 2 years) in the low intensity recreational group. Corresponding figures for those developing a recurrence on entry to the trial, and at the last test before reinfarction, were as follows: 122·6 ± 14·0 and 115·2 ± 14·7 (high intensity endurance group) and 117·4 ± 17·0 and 111·5 ± 17·7 (low intensity recreational group). There was no evidence that the abnormal function of those who had a recurrent infarction was the result of an unusually high proportion of patients treated by beta-blocking agents

Discussion

GENERAL CONSIDERATIONS

Perhaps the most striking feature of this survey is the similarity of patients who reinfarct and those who do not. While our sample undoubtedly includes some patients who had a slow, progressive extension of their disease, in many subjects the second infarction, like the first, was a sudden event, with little clinical or physiological warning. The latter pattern of recurrence is particularly likely in patients receiving exercise rehabilitation, since by selection they tend to be those with a less severe initial episode and a relatively complete restoration of function.

CHARACTERISTICS OF INITIAL EPISODE

The only clue to the likelihood of reinfarction is provided by a history of other previous infarctions. The other features examined (symptoms, electrocardiographic abnormalities, enzyme changes, cardiac arrest, arrhythmia, and minimum systolic blood pressure) might all be expected to relate to the severity of infarction, but nevertheless do not seem to modify subsequent prognosis. There are two possible explanations of this: (i) the referral process and criteria for admission to the multicentre trial may sort out a uniform type of patient, 'suitable' for exercise, who have had an infarction of less than average severity, and (ii) the prognosis may be determined more by residual function than by the characteristics of the previous acute episode.

CLINICAL FEATURES ON ADMISSION TO TRIAL

A previous report (Shephard *et al.*, 1977) noted a number of adverse characteristics. The most important was exercise non-compliance, and others included persistent smoking, angina, ventricular aneurysm, enlarged heart, multifocal ventricular premature beats, exercise ST segment depression, and a serum cholesterol 6·9 mmol/l or more ($\geqslant$ 270 mg/100 ml).

The present study gives limited support to the importance of smoking history ($0{\cdot}1 > P > 0{\cdot}05$) and related symptomatology ($0{\cdot}2 > P > 0{\cdot}01$). The adverse influence of residual disability ($0{\cdot}02 > P > 0{\cdot}01$), shortness of breath ($P < 0{\cdot}001$), and angina of effort ($0{\cdot}1 > P > 0{\cdot}05$) also suggest that exercise non-compliance (Shephard *et al.*, 1977) may be a risk indicator in part because it points to a poor residual myocardial function.

Other investigations (Rechnitzer *et al.*, 1979) suggest that a combination of personality type B, a blue-collar job, and vigorous exercise are associated with a poor prognosis. The present analysis also shows an effect of the type of employment on reinfaction rate ($P < 0{\cdot}001$). It is possible that those in professional and managerial posts are able to adopt a reduced pace of work after infarction, but this option is less available to those in commerce. It is also likely that the professional and managerial groups make greater changes of life style, particularly cessation of smoking, after infarction.

PHYSIOLOGICAL RESPONSES TO EXERCISE

Previous work (Shephard *et al.*, 1977; Shephard, 1979) suggested that one ominous sign of impending reinfarction was inability to develop a normal rise of systolic blood pressure during exercise.

The present study confirms the prognostic importance of a deteriorating myocardial function, the main adverse findings being a low cardiac output during sub-maximal exercise ($P < 0{\cdot}05$)[1], a widening of arteriovenous oxygen difference ($P < 0{\cdot}01$)[1], and poor matching of ventilation and perfusion ($P < 0{\cdot}05$)[1]. None of these indicators is clear cut, presumably because the reinfarctions are of at least two types: (i) a progressive pump failure, and (ii) a sudden ventricular arrhythmia.

Conclusion

The present report has uncovered a few further warnings of vulnerability to reinfarction in patients undergoing exercise rehabilitation. However, with the possible exception of exercise non-compliance (risk ratio 23, Shephard *et al.*, 1977), risk ratios are too low to be of great value in advising individual patients. The safety of exercise rehabilitation will thus continue to rest upon (i) a cautious initial exercise prescription, (ii) gradual progression of activity, and (iii) temporary restriction of activity if there are immediate adverse symptoms (Kavanagh and Shephard, 1973).

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[1] Most significant difference noted during 4 years of observation.

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Haemodynamic effects of a new β_1-receptor agonist in acute myocardial infarction

A useful antidote to unwanted cardiac effects of β-blocking agents

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SUMMARY The haemodynamic effects of a new β_1-receptor agonist, 1-(4 hydroxyphenoxy) 3-isopropylamino-2-propanol, were studied in 25 patients after acute myocardial infarction using non-invasive methods. The drug caused an increase in systolic blood pressure and pulse pressure, without change in diastolic blood pressure, and a slight increase in heart rate and reduction in the pre-ejection period. These changes were greater in patients without a history of left heart failure. It is suggested that this cardioselective drug possesses positive inotropic activity but only slight positive chronotropic activity. The substance has been further investigated as a possible antidote to unwanted cardiac side effects of the cardioselective β-blocker, metoprolol. The changes in the cardiovascular dynamics caused by metoprolol in patients with acute myocardial infarction were promptly reversed by this new β_1-agonist. With its positive inotropic properties and its efficacy in reversing the effects of a cardioselective β-blocker, the drug is a potentially useful pharmacological agent to support an acutely depressed myocardium in patients on β-blocking agents.

Myocardial failure is an important if not a major cause of mortality in acute myocardial infarction, and is related to the size of the infarct (Bolooki *et al.*, 1971) and to the severity of the coronary artery disease (Wackers *et al.*, 1976). Until a definitive form of treatment becomes available, pharmacological support of the failing myocardium is necessary. Beregovich and co-workers (1972) reported that short-term administration of catecholamines improved myocardial contractility after myocardial infarction. These agents, however, may induce undue tachycardia, or arrhythmia (Loeb *et al.*, 1973) and may provoke further myocardial necrosis (Krasnow, 1971; Maroko *et al.*, 1971; Waldenström *et al.*, 1978). Hence, a cardiostimulant drug without these deleterious effects would be a welcome addition to the therapeutic armamentarium.

The substance racemic 1-(4 hydroxyphenoxy)-3-isopropylamino-2 propanol[3] and its laevo form[4], new compounds with β_1-selective agonist activity, were investigated in animals by Carlsson *et al.* (1977) and in healthy volunteers by Johnsson *et al.* (1979) and Knaus *et al.* (1978). Preliminary investigations of their haemodynamic effects, using non-invasive methods in healthy subjects (Johnsson *et al.*, 1979), showed a significant shortening of the pre-ejection period (PEP), left ventricular ejection time (LVET), and electromechanical systole, and a rise in the systolic blood pressure. There were no great changes in heart rate or diastolic blood pressure when the racemic form was given as an intravenous infusion in doses up to 20 μg per kg body weight or in oral doses of 2·5 to 20 mg. These findings indicate a selective inotropic action, making the substance a useful pharmacological agent to support a myocardium whose function has been depressed

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[3] H 80/62, AB Hässle (Astra Pharmaceuticals), Sweden; C_{50} 005/A-Ba, Ciba-Geigy, Switzerland.

[4] H 133/22, AB Hässle (Astra Pharmaceuticals), Sweden; CGP-7760, Ciba-Geigy, Switzerland.

by myocardial infarction or myocardial depressant drugs.

Using non-invasive methods, the haemodynamic effects of the racemic form were studied in patients in a stable phase following acute myocardial infarction. The effects of the laevo form were also studied in patients with acute myocardial infarction after previous intravenous injection of the cardioselective β-blocker metoprolol, to evaluate the drug as a possible antidote to unwanted cardiac effects of β-blocking agents.

Methods

With their informed consent, 25 patients with stable acute myocardial infarction were given 1-(4 hydroxyphenoxy)-3-isopropylamino-2-propanol, using non-invasive procedures. The laevo form of the compound (H 133/22) is twice as potent as the racemic form (H 80/62). The diagnosis of myocardial infarction was based on a typical clinical picture, definite electrocardiographic infarct patterns, and an increase in serum levels of cardiac enzymes (e.g. aspartate aminotransferase, AST). Patient data are shown in Tables 1 and 2.

The first part of the study comprised 15 patients (Table 1), aged from 50 to 80 years, investigated at 2·5 to 21 days from the onset of chest pain. Nine of these patients had a previous history of left ventricular failure and were on diuretics and/or digitalis, but were not in heart failure at the time of the study. None was on β-blocker therapy. After a control period of 20 minutes, to achieve steady state conditions, H 80/62 was infused initially in a dose of 40 to 50 μg per kg body weight. Later, 40 to 50 μg per kg was infused, to give a total dose of 80 to 100 μg per kg body weight. Heart rate was calculated from a continuous electrocardiographic recording, using an average rate during the last 5 minutes before the drug infusion as the control value. Heart rate after infusion of the drug was calculated as mean heart rate during a 5-minute period after completed drug infusion. The blood pressure was measured indirectly every 2 minutes with an ultrasound sphygmomanometer (Arteriosonde 1217, Hoffman La Roche, Inc., Cranbury, USA), which has been shown to give readings which correlate well with the invasively measured blood pressure (Hochberg and Salomon, 1971; George *et al.*, 1975). The systolic and diastolic blood pressures and the pulse pressure were taken as the mean values during a 5-minute period after the completed infusion period. The pre-ejection period (PEP) was measured from simultaneous recordings of the electrocardiogram (lead II), phonocardiogram, and carotid pulse tracing, as previously described (Fabian *et al.*, 1972; Waagstein *et al.*, 1974) and was corrected for heart rate to derive pre-ejection period index (PEPI) (Weissler and Garrard, 1971; Weissler *et al.*, 1972) as an index of myocardial performance.

Table 1 *Clinical features of patients with acute myocardial infarction given H 80/62*

No. of patients	15
Age (y)	50–80 (64·8)
Age of infarct (d)	2·5–21 (9·3)
Maximum AST level (IU/l)*	23–366 (148)
Heart size (ml per m² BSA)	350–850 (496)
Site of infarction	*No. of patients*
Anterior	6
Inferior	8
Unknown	1
History of left heart failure	
Positive	6
Negative	9

* AST (SGOT) normal value ⩽ 17 IU.
All values are shown as range and mean (in parentheses).

Table 2 *Clinical features of patients with acute myocardial infarction given metoprolol and H 133/22*

No of patients	10
Age (y)	36–69 (55·9)
Age of infarct (d)	4–8 (5·8)
Maximum AST level (IU/l)*	31–289 (156)
Heart size (ml per m² BSA)	330–610 (474)
Site of infarction	*No. of patients*
Anterior	6
Inferior	3
Unknown	1

* AST (SGOT) normal value ⩽ 17 IU.
All values are range and mean (in parentheses).

In the second part of the study, 10 patients with acute myocardial infarction (Table 2) were given a cardioselective β-blocking drug, metoprolol (Seloken®, AB Hässle, Sweden), and the laevo form of the inotropic agent (H 133/22). The ages of the patients ranged from 36 to 69 years and they were studied 4 to 8 days after the onset of clinical symptoms of acute myocardial infarction during the stable phase of the disease. Other criteria for inclusion in this group were: (1) no β-blocking therapy within the previous 24 hours; (2) no clinical signs of cardiac failure; (3) systolic blood pressure above 100 mmHg; (4) no signs of poor peripheral circulation; (5) heart rate above 45 beats/minute; and (6) absence of atrioventricular conduction defects.

After a control period of 20 minutes, intravenous metoprolol was administered in 3 doses of 5 mg given at 2-minute intervals. Ten minutes after the metoprolol had been given, H 133/22 was infused continuously for 5 minutes in a dose of 50 μg per kg body weight, using the Braun-Melsungen infusion pump. After the infusion was completed, the patients were monitored until their heart rate and blood pressure reached a steady state. Heart rate, systolic and diastolic blood pressures, pre-ejection period, and pre-ejection period index were measured in the control period, 10 minutes after metoprolol, and 15 and 60 minutes after the end of H 133/22 infusion. The cardiac output was estimated from heart rate and stroke volume, using impedance cardiography (Instrumentation for Medicine, Model 304 A), which has been found to give results which correlate well with those obtained by the Fick method (Naggar *et al.*, 1975). Electrocardiograms were recorded continuously in all patients. No arrhythmias or conduction defects were noted.

Student's t test for paired observations was used for statistical comparisons; values of $P < 0{\cdot}05$ were considered significant.

Results

I: EFFECTS OF H 80/62 IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Intravenous infusion of the drug led to a significant rise in systolic blood pressure without change in the diastolic blood pressure, thus increasing the pulse pressure (Fig. 1 and 2; Table 3). There was a significant but small rise in heart rate and in 2 patients a greater increase was seen (Fig. 3 and 4; Table 3). The pre-ejection period was shortened significantly from the control value (Fig. 5 and 6; Table 3). These changes were already evident at the lower concentration but were larger at the higher dose level. The absence of change in the diastolic blood pressure suggests that the drug has no significant peripheral effect. The decrease in the pre-ejection period corroborates the previous findings in healthy human subjects and indicates positive inotropic activity.

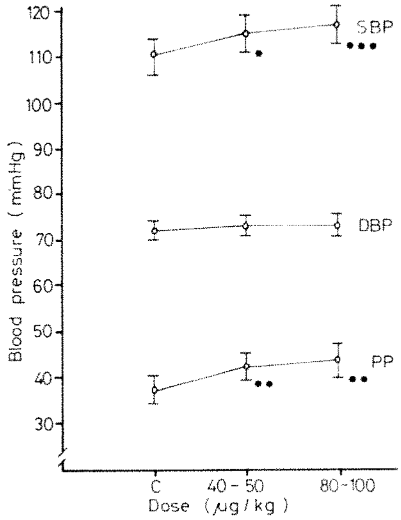

Fig. 1 *Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) in 15 patients with acute myocardial infarction after infusion of H 80/62. All values are shown as mean ± SE.* * $P < 0{\cdot}01$; ** $P < 0{\cdot}001$; *** $P < 0{\cdot}005$.

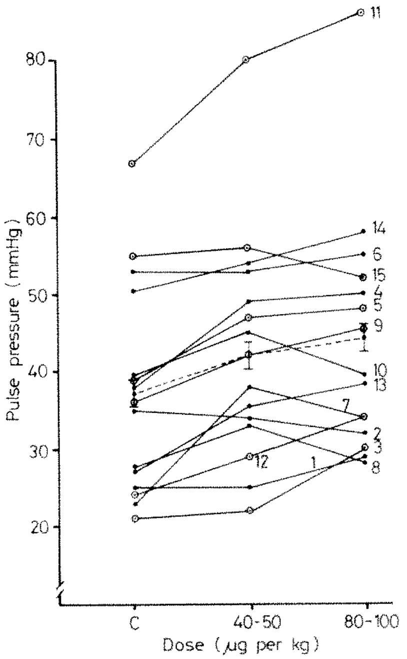

Fig. 2 *Effects of H 80/62 on pulse pressure in 15 patients with acute myocardial infarction.* ● = *acute myocardial infarction with previous left heart failure;* ⊙ = *acute myocardial infarction with no previous left heart failure;* ⫱ = *mean ± SE.*

The responses of the patients with acute myocardial infarction with a history of left heart failure (group 2) were compared with those of patients without left heart failure (group 1) after a dose of 40 to 50 μg per kg body weight of the drug (Table 4). In group 1 there was a significant increase in the pulse pressure and a shortening of the pre-ejection period without significant increase in heart rate. In group 2, however, an increase in the pulse pressure was seen without shortening of the pre-ejection period. Heart rate in this group was significantly increased. The higher dose, 80 to 100 μg per kg

Table 3 *Haemodynamic changes in 15 patients with acute myocardial infarction after infusion of H 80/62*

	Control	*P <*	*H 80/62 (µg per kg body weight)* *40–50*	*P <*	*80–100*
Heart rate (beats/min)	81·1 ±3·8	0·05	84·8 ±4·5	0·02	86·2 ±4·9
Systolic blood pressure (mmHg)	110·7 ±4·4	0·01	115·2 ±4·5	0·005	117·2 ±4·3
Diastolic blood pressure (mmHg)	72·5 ±2·7	NS	72·9 ±2·7	NS	73·0 ±2·6
Pre-ejection period (ms)	104·3 ±4·1	0·01	99·7 ±3·9	0·001	97·8 ±4·6
Pulse pressure (mmHg)	37·6 ±3·6	0·001	43·0 ±3·8	0·001	44·1 ±4·0

All values are shown as mean ± SE. Significance of differences between control and values after administration of 480/62 are shown (P).

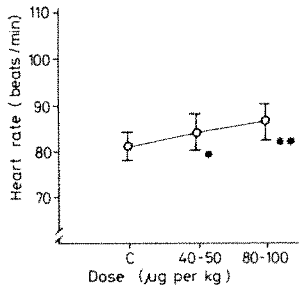

Fig. 3 *Changes in heart rate in 15 patients with acute myocardial infarction after infusion of H 80/62. All values are shown as mean ± SE.* * $P < 0{\cdot}05$; ** $P < 0{\cdot}02$.

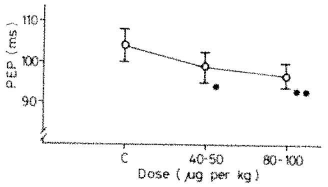

Fig. 5 *Changes in pre-ejection period (PEP) in 15 patients with acute myocardial infarction after infusion of H 80/62. All values are shown as mean ± SE.* * $P < 0{\cdot}01$; ** $P < 0{\cdot}001$.

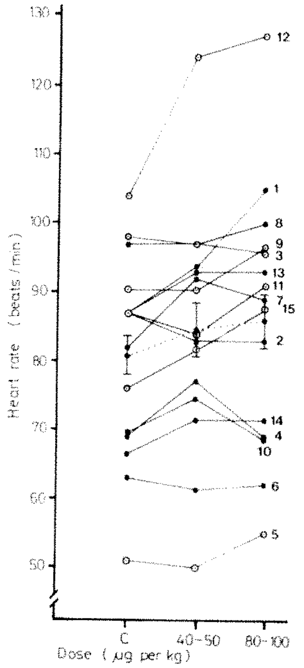

Fig. 4 *Effects of H 80/62 on heart rate in 15 patients with acute myocardial infarction.* ● *=acute myocardial infarction with previous left heart failure;* ⊙ *=acute myocardial infarction with no previous left heart failure;* ⫯ *= mean ± SE.*

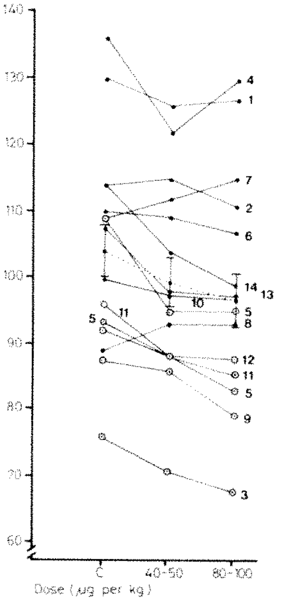

Fig. 6 *Effects of H 80/62 on pre-ejection period (PEP) in 15 patients with acute myocardial infarction.* ● *=acute myocardial infarction with previous left heart failure;* ⊙ *=acute myocardial infarction with no previous left heart failure;* ⫯ *=mean ± SE.*

Table 4 *Comparison of effects of H 80/62 in patients with acute myocardial infarction without left heart failure (group 1) and with left heart failure (group 2)*

	Control	*P <*	*H 80/62 (μg per kg body weight)* *40–50*	*P <*	*80–100*
Group I (n = 6)					
Pulse pressure (mmHg)	40·8 ± 7·4	0·025	46·3 ± 8·5	0·025	49·6 ± 8·2
Heart rate (beats/min)	84·5 ± 7·8	NS	87·9 ± 9·8	0·05	91·8 ± 9·5
Pre-ejection period (ms)	92·4 ± 4·4	0·005	86·2 ± 3·3	0·025	85·4 ± 4·6
Group II (n = 9)					
Pulse pressure (mmHg)	35·6 ± 3·6	0·025	40·7 ± 3·3	0·05	40·1 ± 3·8
Heart rate (beats/min)	78·8 ± 3·9	0·05	82·6 ± 4·1	NS	82·4 ± 1·7
Pre-ejection period (ms)	112·2 ± 4·7	NS	108·6 ± 3·8	NS	108·8 ± 4·8

All values are shown as mean ± SE. Significance of differences between control and values after administration of H 80/62 are shown (P).

body weight, induced further changes in all measurements in group 1 but not in group 2.

II: EFFECTS OF H 133/22 ON PATIENTS WITH ACUTE MYOCARDIAL INFARCTION TREATED WITH METOPROLOL

Metoprolol, a cardioselective β-blocker, in a dose of 15 mg given intravenously, reduced heart rate, systolic and diastolic blood pressures, and pulse pressure (Table 5). It prolonged the pre-ejection period by 9·8 per cent (Fig. 7; Table 5) and caused a reduction in cardiac output with no significant alteration in the stroke volume (Fig. 8 and 9). Fifteen minutes after the infusion of H 133/22 (50 μg per kg body weight during 5 minutes), a significant reversal of the effects of metoprolol was achieved with an increase in heart rate, systolic and diastolic blood pressures, and pulse pressure, and a reduction of the pre-ejection period (Fig. 7; Table 5). Stroke volume was unchanged except in 2 patients (cases 1 and 4), who showed a large increase 15 minutes after the infusion; at 60 minutes the stroke volume returned to the previous level (after metoprolol) in these patients (Fig. 9). Cardiac output increased in all

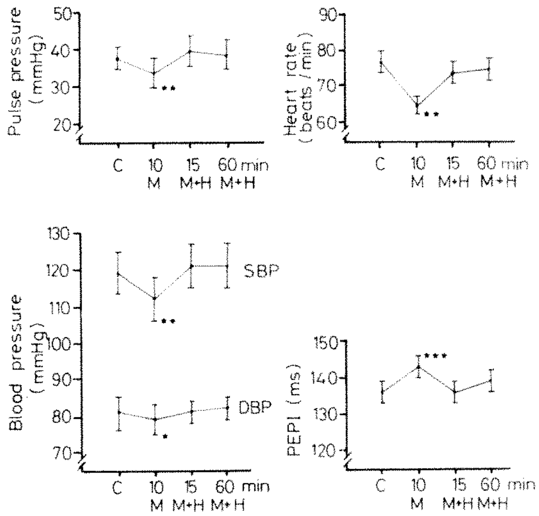

Fig. 7 *Changes in pulse pressure, heart rate, blood pressure, and pre-ejection period index (PEPI) in 10 patients with acute myocardial infarction after infusion of metoprolol (15 mg) (M) and H 133/22 (50 μg per kg body weight) (H). All values shown as mean ± SE.* * *$P<0{\cdot}02$; ** $P<0{\cdot}01$; *** $P<0{\cdot}005$.*

Table 5 *Haemodynamic changes in 10 patients with acute myocardial infarction after metoprolol (15 mg) (M) and H 133/22 (50 μ per kg body weight) (H)*

	Control	*P <* [1]	*10 minutes after M*	*P <* [2]	*15 minutes after H*	*P <* [3]	*60 minutes after H*
Heart rate (beats/min)	76·9 ± 3·1	0·001	65·2 ± 2·4	0·001	74·1 ± 3·2	0·001	75·2 ± 3·3
Systolic blood pressure (mmHg)	119·0 ± 6·0	0·001	112·8 ± 6·4	0·001	120·7 ± 6·3	0·005	120·2 ± 6·4
Diastolic blood pressure (mmHg)	81·0 ± 3·7	0·02	78·5 ± 3·6	0·02	81·0 ± 3·0	0·05	83·3 ± 3·8
Pulse pressure (mmHg)	37·8 ± 3·3	0·001	33·9 ± 3·7	0·001	39·6 ± 4·3	0·005	39·2 ± 3·8
PEP (ms)	106·5 ± 2·5	0·001	117·0 ± 3·0	0·005	107·0 ± 3·5	0·02	109·5 ± 2·9
PEPI (ms)	136·0 ± 2·7	0·005	142·6 ± 3·0	0·02	136·4 ± 3·4	NS	139·1 ± 3·2
LVET (ms)	241·0 ± 7·3	0·001	255·0 ± 6·8	0·001	242·0 ± 7·0	0·005	245·4 ± 6·9
Stroke volume (ml/heart beat)	80·8 ± 4·3	NS	79·4 ± 4·4	NS	79·5 ± 4·9	NS	76·3 ± 4·4
Cardiac output (l/min)	6·17 ± 0·36	0·001	5·02 ± 0·33	0·005	5·87 ± 0·38	0·02	5·69 ± 0·33

All values are shown as mean ± SE.
P values refer to significance of differences between [1] control and 10 minutes after M, [2] 10 minutes after M and 15 minutes after H, [3] 10 minutes after M and 60 minutes after H.

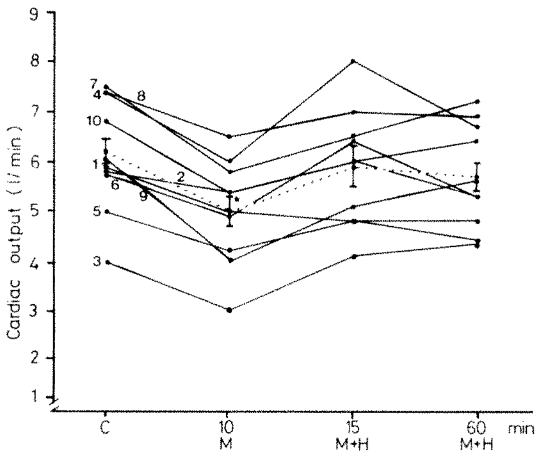

Fig. 8 *Changes in cardiac output in 10 patients with acute myocardial infarction after infusion of metoprolol (M) and H 133/22 (H), as given in Fig. 7. All values are shown as mean ± SE.* * $P < 0{\cdot}001$.

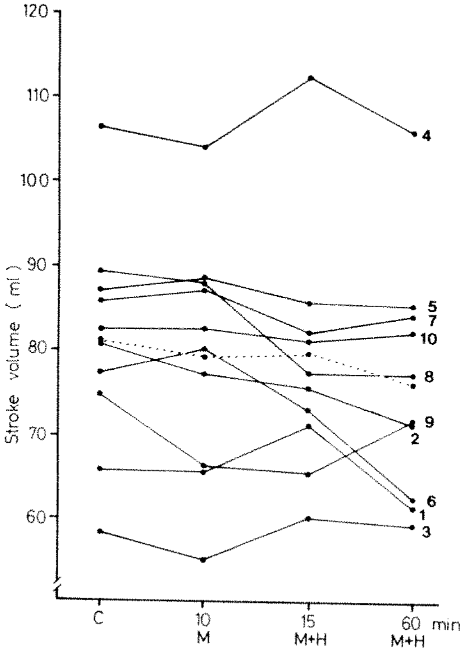

Fig. 9 *Changes in stroke volume in 10 patients with acute myocardial infarction after infusion of metoprolol (M) and H 133/22 (H), as given in Fig. 7. All values are shown as mean ± SE.*

patients after H 133/22 and the values after 15 and 60 minutes were not significantly different from those of the control period (before metoprolol) (Fig. 8; Table 5). All other measurements were also the same 15 and 60 minutes after H 133/22 (Fig. 7–9) as during the control period.

III: ELECTROCARDIOGRAPHIC CHANGES AND SIDE EFFECTS

No arrhythmias or conduction abnormalities were observed in any of the patients before or after the administration of the inotropic compounds during continuous electocardiographic recording. There were no signs of reinfarction in any of the patients as judged from symptoms, repeated daily electrocardiographic recordings, and enzyme analyses. The positive inotropic agent caused no other symptoms and was thus well tolerated.

Discussion

In the first part of this investigation, the haemodynamic effects of racemic 1-(4 hydroxyphenoxy)-3-isopropylamino-2-propanol (H 80/62) were studied on patients with acute myocardial infarction using non-invasive methods. The results showed an improvement in cardiac contractility, as shown by a reduction in the pre-ejection period, an increase in heart rate, and a rise in the systolic blood pressure and pulse pressure, effects similar to those of other β-adrenergic agonist compounds (Harris *et al.*, 1967; Krasnow, 1971; Weissler and Garrard, 1971). In contrast to isoprenaline, which has both cardiac (β_1) and peripheral (β_2) effects, H 80/62 did not affect the peripheral vessels, as shown by an unchanged diastolic blood pressure, as was noted by Carlsson *et al.* (1977) in the intact animal.

The insignificant reduction of pre-ejection period in patients with a history of left heart failure is probably the result of decreased sensitivity of β_1-receptors mediating changes in contractility, as is seen in patients with chronic heart failure (Thomas and Marks, 1978). Some of these patients might need higher doses of the drug in order to respond with increased contractility. Some patients might not react at all to inotropic stimulation because of the severity of myocardial dysfunction. Dogs with failing hearts seem to react with an increased chronotropic response rather than an increased inotropic response to catecholamines, compared with controls (Newman, 1977). From the present study, it may be concluded that the drug possesses cardioselective agonist properties with only moderate chronotropic activity. These properties, in the absence of arrhythmic effects, may make the drug preferable to other sympathetic agonists for pharmacological support of the depressed myocardium.

In the second part of the study, the infusion of

50 μg per kg of H 133/22 completely reversed the effects of the β-blocking agent metoprolol (15 mg i.v.) in patients with acute myocardial infarction. In acute myocardial infarction, β-blocking drugs are administered to counteract the harmful effect of increased endogenous catecholamines on cardiac metabolism and cardiac work (Maroko *et al.*, 1971; Videbaek *et al.*, 1972; Waagstein and Hjalmarson, 1975; Waldenström *et al.*, 1978). Under certain circumstances, however, an unexpected depression of cardiac performance may occur, resulting in a drop in blood pressure and cardiac output, requiring immediate treatment. It has been found that β-blocking drugs are effective in controlling angina pectoris (Ekelund *et al.*, 1976), reducing ischaemic injury (Maroko *et al.*, 1971; Reimer *et al.*, 1973; Waagstein *et al.*, 1974; Gold *et al.*, 1976), controlling hypertension and certain arrhythmias (Jewitt and Singh, 1974), and in treatment of hyperkinetic circulatory states (Frohlich, 1971). An increasing number of patients on chronic β-blocker treatment will therefore be seen in emergency situations, such as acute myocardial infarction during surgical procedures. Sudden withdrawal of the β-blocker removes its protective effect on the ischaemic myocardium and its preventive effect against arrhythmias. The sudden withdrawal of β-blockers may be harmful (Miller *et al.*, 1975). The present investigation indicates that β-blocker treatment does not necessarily have to be withdrawn abruptly in these patients in emergency situations since an effective antidote is available for prompt reversal of the unwanted depression of cardiac function by β-blockade.

Isoprenaline and noradrenaline have been widely used to reverse the adverse effects of β-blocking agents. In a recent study it was found that dobutamine could reverse all the effects of the β-blocking agent metoprolol in patients with acute myocardial infarction (Waagstein *et al.*, 1978). From animal experiments (Robie *et al.*, 1974) it is known that dobutamine, in addition to its β_1-stimulating action, also has α-receptor and β_2-receptor stimulating effects. Low or moderate doses of dobutamine have balanced effects on vasoconstriction and vasodilatation with small changes in peripheral vascular resistance (Akhtar *et al.*, 1975; Loeb *et al.*, 1975). However, in situations where very high doses of dobutamine have to be given to overcome the adverse effects of β-blockade, the peripheral action of dobutamine could be of importance. During treatment with nonselective β-blocking agents, α-receptor effects of dobutamine may be unmasked, resulting in a large increase in peripheral vascular resistance. For this reason, a β_1-stimulating drug such as H 133/22, with no peripheral action, is preferable to drugs like isoprenaline, noradrenaline, dobutamine, and dopamine, especially when this is given to counteract adverse effects of a non-cardioselective β-blocker.

The effective reversal of the cardiovascular effects of metoprolol by H 133/22 makes it valuable in counteracting the cardiodepressant effect of β-blockers, especially β_1-blocking agents. Because of its greater inotropic than chronotropic effect, it may be of value also in the treatment of congestive heart failure and hypotension. The combination of digitalis and H 133/22 with balanced effects on heart rate and optimal positive inotropic stimulation seems promising for the long-term treatment of patients with heart failure. The lack of arrhythmogenic properties also makes it useful in the treatment of extreme bradycardia and atrioventricular conduction. A special advantage of this inotropic agent compared with others available is that the drug can be given orally. Studies of the clinical value of the drug in acute and long-term treatment are in progress.

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Assessment of pulmonary valve echogram in normal subjects and in patients with pulmonary arterial hypertension

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SUMMARY To assess the validity of ultrasound criteria for pulmonary arterial hypertension, we studied pulmonary valve motion in 28 patients and 20 normal subjects. In the latter group, we categorised normal movement of the posterior leaflet of the pulmonary valve in a fashion not previously described. Of the 28 patients, 19 had pulmonary arterial hypertension (pulmonary artery mean pressure more than 20 mmHg, range 22 to 72). Negative, flat, and positive e to f slopes occurred equally in normal subjects and patients. Maximal a wave excursion was less than 2 mm in 9 of 13 patients with pulmonary hypertension who had sinus rhythm, but was more than 2 mm in all normals and in the 9 patients with normal pulmonary artery pressure (69% sensitivity and 100% specificity). The b to c slope was more than 450 mm/s in 6 of 18 patients with pulmonary arterial hypertension and was less than 450 mm/s in all others (33% sensitivity and 100% specificity). The normalised right ventricular pre-ejection period was more than 0·095 (range 0·10 to 0·16) in 13 of the 19 patients with pulmonary arterial hypertension and less than 0·095 in all others (68% sensitivity and 100% specificity). A midsystolic notch occurred in patients with pulmonary arterial hypertension and in no normal subjects or patients with normal pulmonary arterial pressure. Of the 19 patients with pulmonary arterial hypertension, 18 were identified by one or more ultrasound criteria. Of the 5 patients who met only 1 criterion (increased normalised right ventricular pre-ejection period), 4 had atrial fibrillation. We conclude that measurement of the pulmonary valve e to f slope is useless for identifying pulmonary arterial hypertension. However, changes in normalised right ventricular pre-ejection period, maximal a wave excursion, b to c slope, and the presence of a midsystolic notch, while insensitive, are highly specific for pulmonary atrial hypertension.

The pulmonary valve remains the most elusive and difficult valve from which to record echocardiograms, particularly in normal subjects. There have been a number of studies of the changes in the pulmonary valve echogram in patients with pulmonary arterial hypertension (Nanda *et al.*, 1974; Weyman *et al.*, 1974b; Kaku *et al.*, 1978). The present investigation was undertaken to evaluate the previously described ultrasound criteria for pulmonary arterial hypertension, and to assess normal and abnormal variations in pulmonary valve motion on the echocardiogram.

Subjects

Twenty-one men, aged 17 to 74 years (mean 47) and 7 women, aged 19 to 70 years (mean 51) were studied by echocardiography and cardiac catheterisation. Satisfactory pulmonary valve echograms were recorded in all 28 patients. Twenty-two of the patients were in sinus rhythm and 6 had atrial fibrillation. The diagnosis was valvar heart disease in 13 patients, congenital heart disease in 3, coronary artery disease in 2, pulmonary emboli in 2, cardiomyopathy in 2, primary pulmonary hypertension in 1, and no cardiopulmonary disease in 5 patients. The interval between echocardiogram and cardiac catheterisation was 0 to 7 days (mean 1·6) in 23 of the 28 patients. In the remaining 5 patients, the interval was 2 weeks to 3 months (mean 42 days),

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but during this time there was no evident change in their clinical condition.

Of the 28 patients who had cardiac catheterisation studies, 9 had a normal pulmonary artery mean pressure of 20 mmHg or less. All 9 were in sinus rhythm. Nineteen patients, 13 of whom were in sinus rhythm, had raised pulmonary artery (PA) mean pressure (more than 20 mmHg, range 22 to 72 mmHg). Nine of these patients had a raised right ventricular end-diastolic pressure (RVEDP) more than 10 mmHg (range 11 to 16 mmHg).

Twenty normal subjects were studied by echocardiography alone. In all 20 the pulmonary valve was well visualised. This group included 15 men, aged 23 to 34 years (mean 27) and 5 women, aged 24 to 26. None of the normal subjects had any evidence of cardiopulmonary disease by history, physical examination, electrocardiogram, or echocardiography.

Methods

Echocardiograms were obtained with a commercially available device.[1] A medium internal focus 2·26 MHz transducer with a repetition rate of 1000 impulses/s was used. The technique for recording the pulmonary valve echo has been previously described (Gramiak *et al.,* 1972; Weyman *et al.,* 1974a). All 20 normal subjects were studied in the left lateral position. The optimal echocardiographic 'window' in normal subjects was in the fourth intercostal space in 19 and the third intercostal space in 1. Of the 28 patients, 24 were studied in the left lateral position; 19 had recordings in the fourth intercostal space, 4 in the third intercostal space, and 1 in the second intercostal space. The remaining 4 patients were studied in the supine position in the fourth intercostal space.

At least 5 beats displaying the pulmonary valve echogram were recorded in each of the 48 subjects and patients, with a simultaneous lead II electrocardiogram. The normal motion of the pulmonary valve is shown in Fig. 1–3. The posterior leaflet of the pulmonary valve moves in a flat or posterior fashion from points e to f (Fig. 1). The rate of this motion is measured as the e–f slope (mm/s). The f point marks the beginning of the a dip and coincides with the end of the P wave on the electrocardiogram. The a wave excursion is measured as the vertical displacement between the f point and the trough of the a dip (Fig. 2). There are respiratory variations in this measurement and the maximum a wave excursion (A_{max}) is the measurement used for comparative purposes. At the end of the a excursion, the posterior leaflet of the pulmonary valve moves slightly anteriorly to the b point which corresponds to the initiation of right ventricular ejection and therefore with pulmonary valve opening. It then opens rapidly to the posteriorly located c point (Fig. 3). The most rapid motion occurs towards the end of this b–c segment and is measured as the b–c slope (mm/s). The vertical displacement between points b and c is measured as the b–c opening distance or amplitude.

The systolic movements of the posterior leaflet of the pulmonary valve are not normally recorded. When they are visible there is an anterior motion from c to the d point, followed by pulmonary valve closure from d to e. Occasionally, midsystolic notching is present giving the systolic pulmonary valve echo a 'W' configuration. Under these circumstances, the posterior leaflet moves anteriorly early in systole followed by a posterior motion and

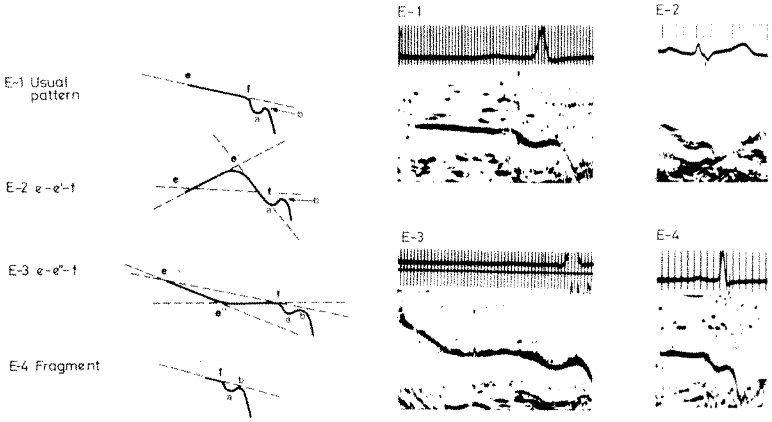

Fig. 1 *Normal variations in the pulmonary valve e–f slope. On the left, the dotted lines indicate in diagrammatic fashion the various ways of measuring the e–f slope. Actual recordings for each of the patterns are shown on the right.*

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[1] Picker Echoview System 80C coupled to an Irex Continu-Trace unit for display and recording.

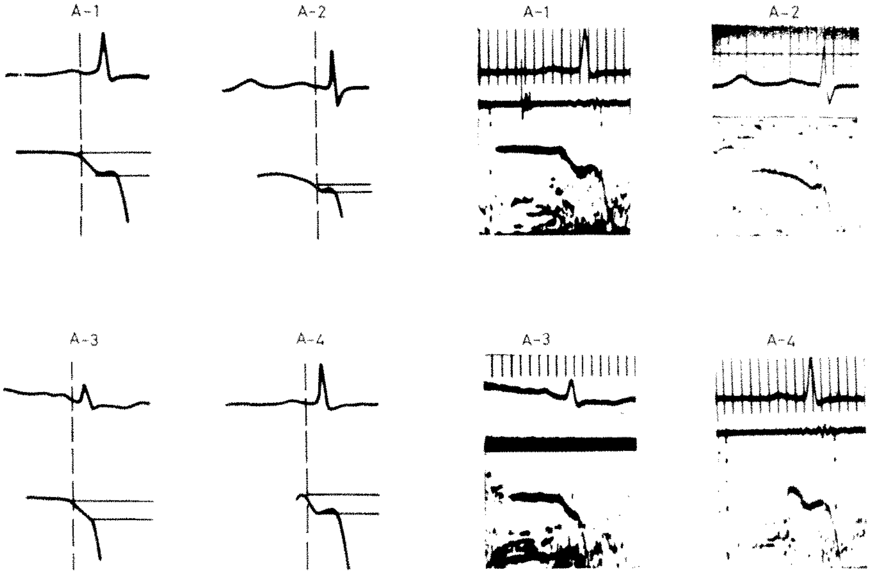
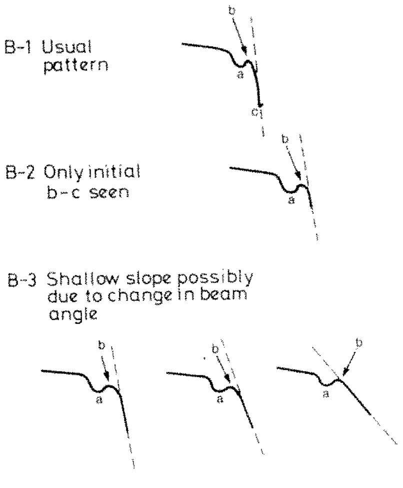


Fig. 2 *Measurement of A_{max}. On the left, the dotted vertical lines indicate the onset of the dip at the end of the P wave of the electrocardiogram. The horizontal lines depict the maximum depth of the a dip (A_{max}). In the panels on the right, actual recordings for each of the patterns are shown.*


B-1 Usual pattern
b
a
c
B-2 Only initial b-c seen
b
a
B-3 Shallow slope possibly due to change in beam angle
b
a
b
a
b
a

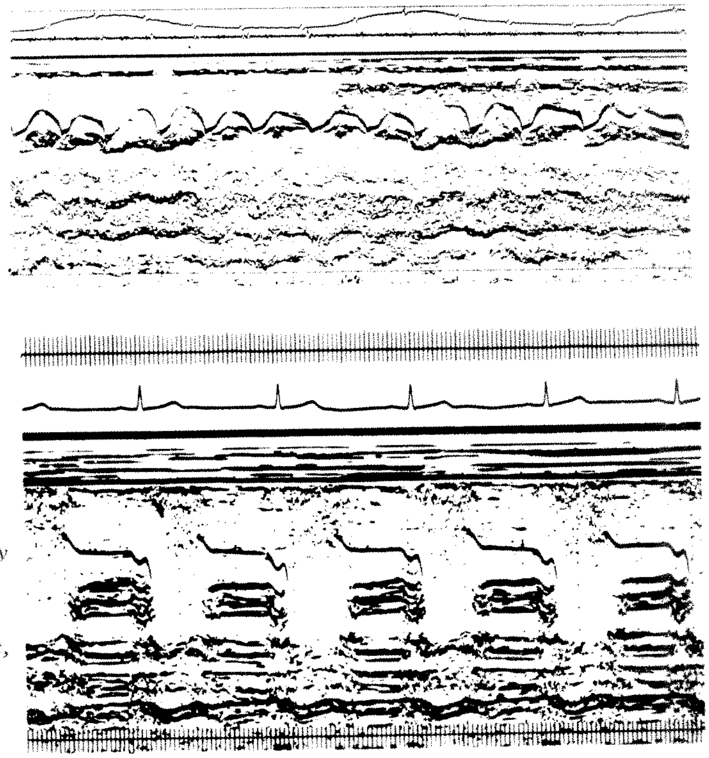


Fig. 3 *Normal variations in the pulmonary valve b–c slope. On the left, the normal variations in the b–c slope are shown in diagrammatic fashion. In the echocardiographic tracing at the upper right, the pulmonary valve b–c slope can be seen to vary with phase of respiration (altered beam angle). The right lower panel is characteristic of pattern B-2.*

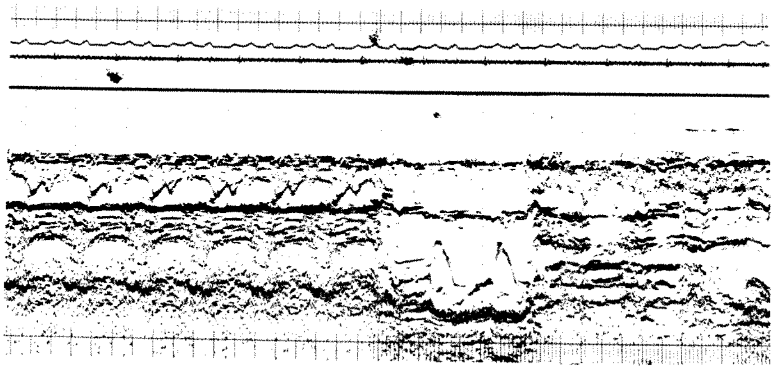


Fig. 4 *An echocardiographic sweep showing portions of the pulmonary and mitral valves. The pulmonary valve recording at the upper left portion of the recording shows 'notching' characteristic of pulmonary arterial hypertension.*

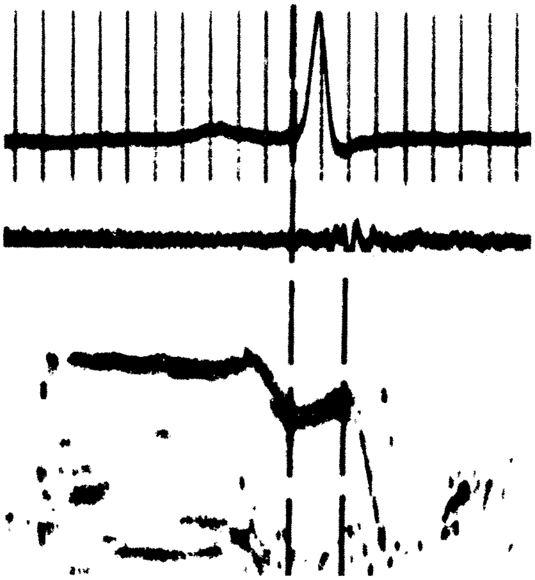


Fig. 5 *Measurement of right ventricular pre-ejection period (RPEP). The dotted line on the left identifies the onset of the QRS complex of the electrocardiogram, and the one on the right indicates the onset of pulmonary valve opening. The time between the two lines measures RPEP, which in the example shown is 80 ms.*

then another anterior motion during pulmonary valve closure (Fig. 4).

Right ventricular systolic time intervals were obtained by methods previously described (Nanda *et al.*, 1974; Hirschfeld *et al.*, 1975). The right ventricular pre-ejection period (RPEP) was measured between the time of onset of electrical and mechanical right ventricular systole, that is from the onset of the QRS complex on the electrocardiogram to the b point of the pulmonary valve echo (Fig. 5). Normalised right ventricular pre-ejection period was calculated as $\text{RPEP}/\sqrt{\text{R-R}}$, where R-R is the cycle length in seconds (Nanda *et al.*, 1974). The right ventricular ejection time (RVET) was measured between the b point and the point of pulmonary valve closure (Hirschfeld *et al.*, 1975) but could only be recorded in 9 patients with pulmonary hypertension and in none of the other patients or normal subjects. The ratio of the RPEP to the RVET was also calculated.

Results

PULMONARY VALVE ECHOGRAM IN NORMAL SUBJECTS

e–f slope

In normal individuals variations in the e–f slope, a excusion, and b–c slope occurred commonly (Fig. 1). The e–f slope occasionally moved anteriorly to an e′ position followed by normal posterior motion (Fig. 1, E-2), or it moved posteriorly to e″ followed by a long flat e–f segment (Fig. 1, E-3). In both cases the terminal segment preceding the a excursion was measured as the e–f slope. In some cases only the terminal e–f segment was visualised (Fig. 1, E-4).

A_{max}

The most common a dip was classified as A-1 (Fig. 2). In this pattern there is a well-defined f point initiating the a excursion and a return anteriorly to the b point at the end of the a excursion. In pattern A-2 the end of the P wave on the electrocardiogram arbitrarily defined the f point and thus the height of the a excursion, since the e–f slope merged continuously into the trough of the a dip (Fig. 2, A-2). Where the P wave is not well defined on lead II of the electrocardiogram, a different standard lead should be employed. Nevertheless, even under the best of circumstances, this pattern may lead to inaccuracies in the measurement of A_{max}. In pattern A-3 there was a distinct

Table 1 *Echocardiographic values in normal subjects*

Case no.	*Age/sex*	*Rate (bpm)*	*e–f slope (mm/s)*	*b–c slope (mm/s)*	A_{max} *(mm)*	*b–c amplitude (mm)*	*RPEP (s)*	*R-R and* $\sqrt{R\text{-}R}$	$\frac{RPEP}{\sqrt{R\text{-}R}}$
1	26/F	82	12·0	407	3·8	9·8	0·063	0·732 0·856	0·073
2	34/M	58	4·9	328	3·7	—	0·069	1·036 1·018	0·067
3	26/M	58	4·5	441	4·5	—	0·057	1·036 1·018	0·056
4	26/F	58	1·1	312	3·7	—	0·071	1·042 1·02	0·069
5	32/M	53	0·6	307	2·3	—	0·047	1·141 1·068	0·044
6	24/M	66	0·9	409	4·3	—	0·056	0·910 0·954	0·058
7	23/M	71	9·2	358	3·9	—	0·082	0·843 0·918	0·089
8	30/M	66	3·0	357	4·5	—	0·071	0·913 0·956	0·075
9	30/M	60	2·3	307	4·0	8·2	0·064	1·003 1·0	0·064
10	26/F	63	0·1	316	3·9	—	0·052	0·946 0·973	0·054
11	26/M	63	6·4	284	3·2	—	0·067	0·957 0·978	0·068
12	30/M	63	2·1	335	3·7	—	0·073	0·946 0·973	0·075
13	25/M	73	−5·0	302	3·5	—	0·073	0·823 0·907	0·080
14	23/M	55	0·2	208	4·2	8·9	0·092	1·10 1·05	0·088
15	24/M	31	2·2	—	2·7	—	0·069	1·923 1·387	0·050
16	24/M	51	1·4	314	5·1	11·7	0·071	1·179 1·086	0·065
17	25/M	53	0·4	388	7·2	11·9	0·068	1·139 1·18	0·058
18	25/M	58	2·8	288	3·2	11·9	0·068	1·04 1·02	0·067
19	26/F	57	0·8	336	6·3	11·2	0·059	1·047 1·023	0·058
20	24/F	54	0·7	263	3·4	10·2	0·078	1·109 1·053	0·074

RPEP, right ventricular pre-ejection period; R-R, interval between beats (s).

f point and a dip, but at the end of the a dip the pulmonary valve does not return to an anterior position before opening. This phenomenon has been described as a result of normal inspiration (Weyman *et al.*, 1974a), but in some of our studies the posterior leaflet of the pulmonary valve never returned to an anterior position even during expiration. In these instances the posterior leaflet opened from a partially open or domed position at the end of diastole and occasionally gave the appearance of an absent a dip. In such cases A_{max} was measured from the f point to the plateau of the a dip before the valve opened fully. In Fig. 2 the illustration for pattern A-3 shows a PR interval of 0·12 s but none of the other 3 subjects had PR intervals less than 0·14 s. In group A-4 there is a clear a dip but an incomplete e–f slope as in Fig. 2. In this group the end of the P wave of the electrocardiogram was used to define the f point and the height of the a dip.

b–c slope

The b–c slope also varied according to the portion of the b–c segment visualised. The b–c slope was designated as B-1 when the entire opening of the pulmonary valve was seen (Fig. 1, E-4, Fig. 2, A-1). That full valve opening had occurred was confirmed by visualising the characteristic abrupt change in direction of the echo produced by rapid anterior motion at the c point (Fig. 3, B-1). The most rapid movement occurred late in the b–c segment so that visualisation only of the earlier portion gave slower b–c slope measurements (Fig. 3, B-2). Variation in b–c slope also occurs with differing cycle lengths,

Table 2 *Echocardiographic and haemodynamic data in patients*

Case no.	*Age/sex*	*Rhythm*	*Heart rate (bpm)*	*e–f slope (mm/s)*	*b–c slope (mm/s)*	A_{max} *(mm)*	*b–c amplitude (mm)*	*Midsystolic notching*	*RPEP (s)*	*R-R and* $\sqrt{R\text{-}R}$
1	25/M	NSR	72	−12·1	392	4·4	—	No	0·067	0·830 0·91
2	20/M	NSR	81	2·8	171	6·9	10·4	No	0·060	0·739 0·86
3	74/M	NSR	54	—	394	6·7	—	No	0·059	1·107 1·05
4	51/M	Sinus bradycardia	48	—	380	2·2	—	No	0·066	1·242 1·11
5	17/M	NSR	95	7·6	445	2·8	—	No	0·063	0·634 0·79
6	46/M	NSR	64	−5·3	408	3·7	—	No	0·087	0·934 0·96
7	67/M	NSR	59	0·9	243	5·0	—	No	0·069	1·024 1·01
8	57/M	NSR	58	2·4	299	2·0	12·3	No	0·080	1·033 1·02
9	45/M	NSR	76	−2·1	259	2·4	—	No	0·066	0·789 0·89
10	52/M	NSR	92	—	609	5·2	17·3	No	0·075	0·652 0·808
11	59/F	NSR	68	6·6	327	2·4	—	No	0·098	0·880 0·938
12	55/M	NSR	56	−1·0	287	2·4	—	No	0·094	1·081 1·04
13	59/M	NSR	60	13·9	413	0	6·3	Yes	0·088	1·0 1·0
14	73/M	NSR	106	2·5	392	0	10·0	No	0·103	0·566 0·752
15	44/M	NSR	92	1·0	363	0	—	No	0·088	0·650 0·806
16	25/M	NSR	72	9·5	321	1·9	—	No	0·115	0·834 0·911
17	63/M	NSR	73	7·2	346	0	—	No	0·093	0·826 0·909
18	31/M	NSR	70	1·9	270	0·9	13·7	Yes	0·060	0·855 0·924
19	28/M	NSR	39	6·2	503	2·3	14·5	Yes	0·111	1·546 1·24
20	46/M	NSR	80	7·3	394	0	19·4	Yes	0·090	0·746 0·86
21	28/F	NSR	119	0·1	478	0	8·5	Yes	0·088	0·506 0·711
22	19/F	NSR	90	27·0	495	0	12·1	No	0·059	0·670 0·819
23	70/F	Atrial fib.	71	3·3	466	0	—	No	0·102	0·843 0·918
24	66/F	Atrial fib.	95	5·6	368	0	6·3	No	0·123	0·630 0·794
25	71/M	Atrial fib.	76	12·7	399	0	12·1	No	0·141	0·786 0·887
26	46/F	Atrial fib.	107	27·0	284	0	—	No	0·116	0·563 0·750
27	68/F	Atrial fib.	91	5·5	—	0	—	No	0·098	0·663 0·814
28	38/M	Atrial fib.	102	13·5	555	0	15·1	No	0·120	0·590 0·768

NSR, normal sinus rhythm; RPEP, right ventricular pre-ejection period; R-R, interval between beats (s); RVET, right ventricular ejection time; PA, pulmonary artery; S/D, systolic/diastolic; M, mean; RV, right ventricular; ED, end-diastolic; CAD, coronary artery disease; PS, pulmonary stenosis; AR, aortic regurgitation; ASD, atrial septal defect; MS, mitral stenosis; PH, pulmonary hypertension; PE, pulmonary emboli; AS, aortic stenosis; MR, mitral regurgitation; 1°PH, 'primary' pulmonary hypertension; VSD, ventricular septal defect; MVR, mitral valve replacement.

$\frac{RPEP}{\sqrt{R\text{-}R}}$	*RVET*	$\frac{RPEP}{RVET}$	*Diagnosis*	*PA pressure, mmHg S/D (m)*	*RV pressure, mmHg S/ED*
0·073	—	—	Normal	24/5 M = 10	23/2
0·063	0·338	0·179	Normal	16/7 M = 11	27/5
0·056	—	—	CAD	19/8 M = 12	20/7
0·059	—	—	Normal	22/10 M = 14	29/6
0·080	—	—	Valvular PS	22/12 M = 16	45/11
0·091	—	—	Normal	28/12 M = 18	28/10
0·068	—	—	AR	33/11 M = 20	32/7
0·079	—	—	Normal	23/10 M = 15	25/7
0·074	—	—	CAD	23/14 M = 16	25/5
0·093	—	—	ASD	27/14 M = 22	32/5
0·104	—	—	MS	33/19 M = 24	37/4
0·091	—	—	AR	38/18 M = 24	39/14
0·088	0·373	0·22	PH, PE	46/19 M = 27	49/8
0·137	0·230	0·45	AS, CAD	31/10 M = 28	36/5
0·109	—	—	MR	52/22 M = 31	50/5
0·126	0·274	0·42	Cardio-myopathy	60/30 M = 39	60/14
0·102	—	—	MR, CAD	64/30 M = 40	63/9
0·065	0·432	0·14	PH, PE	74/25 M = 43	74/11
0·090	—	—	1°PH	78/40 M = 55	78/15
0·105	0·371	0·244	ASD	88/40 M = 55	88/4
0·124	0·207	0·426	MS	104/50 M = 72	104/16
0·072	—	—	VSD	60/29 M = 43	61/9
0·111	—	—	MS/CAD	43/13 M = 26	46/4
0·155	0·194	0·63	MS	48/22 M = 33	52/5
0·159	0·275	0·515	AS/MS/MR/CAD	65/30 M = 38	65/12
0·155	—	—	MVR	53/29 M = 40	52/11
0·120	—	—	MS	83/31 M = 52	83/12
0·156	0·255	0·48	Cardio-myopathy	67/45 M = 58	65/14

phase of respiration, and/or transducer placement as in Fig. 3, B-3. In all cases the most rapid slope was measured.

MEASUREMENTS IN NORMAL SUBJECTS AND IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION (Tables 1, 2)

e–f slope

The pulmonary valve e–f slope was compared with the PA mean pressure (Fig. 6). In 20 normal subjects the e–f slope had a mean value of 2·4 ± 3·7 mm/s (SD) with a range of –5·0 to 12·0 mm/s. The mean value for the patients with pulmonary arterial hypertension was 8·3 ± 8·1 mm/s which was higher than for the normal subjects ($P < 0·006$), but the overlap in values was too great to allow any separation between groups.

A_{max}

A_{max} was measured in all 48 subjects. The relation between A_{max} and PA mean pressure is shown in Fig. 7. There is a general inverse relation showing that higher PA mean pressures are associated with lower values of A_{max}. The 20 normal subjects had a mean A_{max} of 4·1 ± 1·1 mm with a range of 2·3 to 7·2 mm. The 9 patients with normal PA mean pressures had A_{max} values ranging from 2·0 to 6·9 mm with mean A_{max} nearly identical to that for the normal subjects (Fig. 7). Thus, A_{max} was 2·0 mm or greater in all 29 normal subjects and patients with a normal PA mean pressure (100%).

In the 13 patients with raised PA mean pressure and sinus rhythm, the mean A_{max} was 1·2 ± 1·6 mm (range of 0 to 5·2 mm). The mean was lower than in the normal subjects ($P < 0·001$). A_{max} was zero in 7 of the 13 patients (54%), between 0 and 2 mm in 2 (both also had an elevated RVEDP), and exceeded 2 mm in 4 (2 of these also had an elevated RVEDP). Thus, there were 9/13 (69%) who had A_{max} values of less than 2 mm whereas in all the normal subjects A_{max} exceeded 2 mm. Therefore, an A_{max} of less than 2 mm had 100 per cent specificity and 69 per cent sensitivity as a criterion for pulmonary arterial hypertension. Of the 4 false negatives (those with pulmonary hypertension who had an A_{max} value of 2 mm or greater), 3 had only slightly raised PA mean pressures (22 to 24 mmHg). Thus, of the 10 patients with PA mean pressures of 25 mmHg or greater, 9 (90%) had A_{max} values of less than 2 mm.

As might be expected, all 6 patients with pulmonary hypertension and atrial fibrillation had no a dip.

b–c slope

The b–c slope was measured in 96 per cent (46/48) of subjects, and is compared with the PA mean pressure in Fig. 8. In 19 normal subjects, the mean b–c slope was 328 ± 55 mm/s (range 208 to 441 mm/s). Mean b–c slope in the 9 patients with normal PA mean pressure was nearly identical to that in the normal subjects. The 18 patients with pulmonary arterial hypertension in whom the b–c slope was measured had higher values (mean 403 ± 96 mm/s, range 270 to 609 mm/s) ($P < 0·007$). A rapid b–c slope of 450 mm/s or more was found

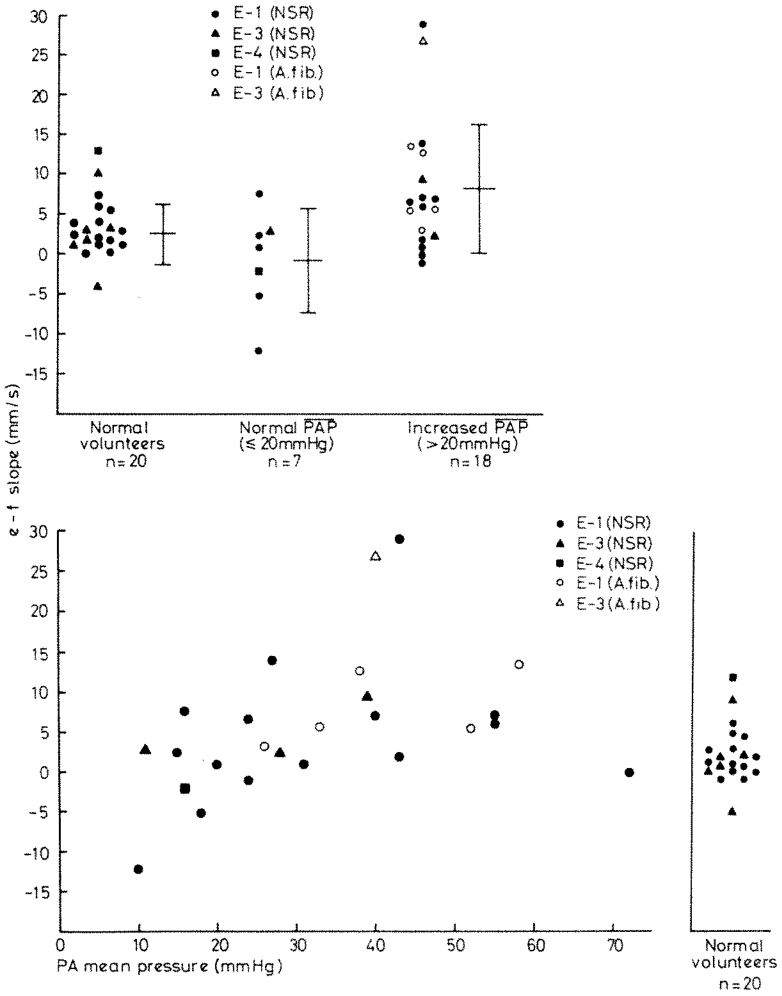


Fig. 6 *Individual e–f slope data. In the upper panel mean value ± 1 standard deviation is shown for each group. In the lower panel it can be seen that there is a rough correlation between the e–f slope and PA mean pressure, but the scatter is too great to be of any predictive value. There is also no relation between any of the e–f slope patterns (E1–4) and PA pressure.* $\overline{PAP}$*, pulmonary artery mean pressure; NSR, normal sinus rhythm; A. fib., atrial fibrillation.*

only in patients with raised PA mean pressure and was thus 100 per cent specific for pulmonary arterial hypertension. The sensitivity was 33 per cent since only 6 of the 18 patients with pulmonary hypertension had such rapid b–c slopes.

b–c opening amplitude

The b–c opening amplitude was measured in 44 per cent (21/48) of all subjects, and is plotted against PA mean pressure in Fig. 9. The 8 normal subjects had values from 8·2 to 11·9 mm (mean 10·5 ±1·4 mm). There was no significant difference between normal subjects and the 11 patients with raised PA mean pressure who had a mean value of 12·3 ±4·3 mm (Fig. 9). However, none of the normal subjects had b–c opening amplitudes greater than 13 mm whereas 5 of 11 (45%) with pulmonary hypertension met this criterion. When an abnormally large b–c opening amplitude greater than 13 mm was used as a criterion for pulmonary arterial hypertension, there was 100 per cent specificity and 45 per cent sensitivity.

Midsystolic notching

Midsystolic notching was not seen in any of the 20 normal subjects, in the 9 patients with normal PA mean pressure, or in the 9 patients with raised PA mean pressure and atrial fibrillation. Midsystolic notching (Fig. 4) was present in 5 of the 13 (38%) patients with raised PA mean pressure who were in sinus rhythm. Thus, for this last group there was 100 per cent specificity, with 38 per cent sensitivity. Five of these 13 patients had PA mean pressures ranging from 43 to 72 mmHg and midsystolic

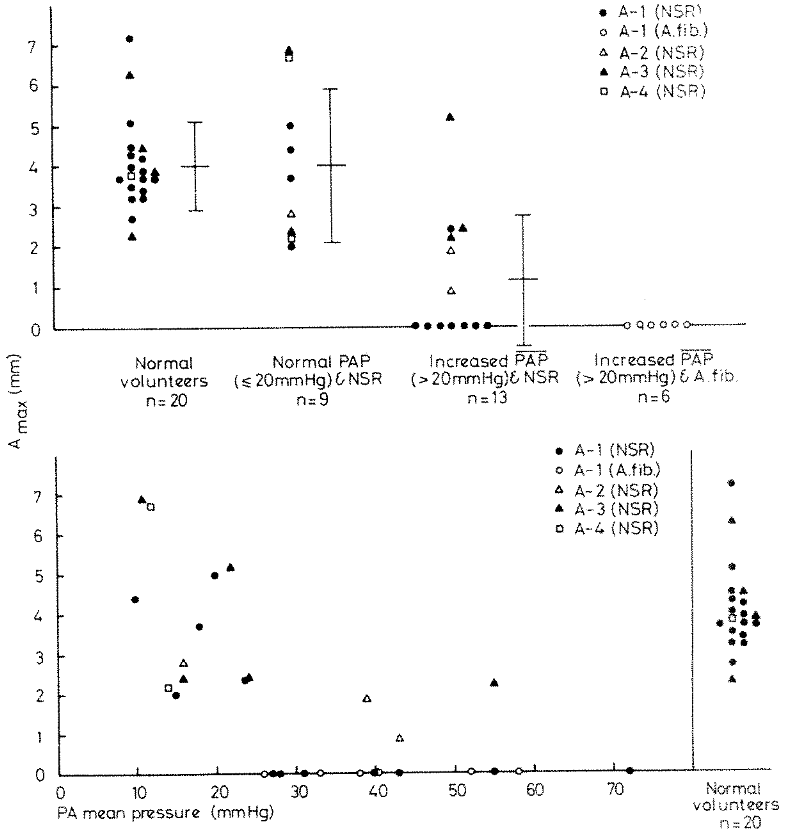


Fig. 7 *Individual data for maximal* a *wave excursion* (A_{max}). *Most of the patients with sinus rhythm and an increased mean pulmonary artery pressure had an* A_{max} *value of less than 2 mm* (upper panel). *There is, however, no relation between any of the a wave patterns (A1–4) and PA pressure.* $\overline{PAP}$, *pulmonary artery mean pressure; NSR, normal sinus rhythm; A. fib., atrial fibrillation.*

notching was present in all but one of these (PA mean pressure 43 mmHg). Midsystolic notching was also present in the 4 patients with the highest PA systolic pressures (74 to 100 mmHg).

Right ventricular pre-ejection period
The right ventricular pre-ejection period (RPEP) was measured in all 48 subjects, and is compared with the PA mean pressure in Fig. 10, which shows a prolongation in RPEP at higher PA mean pressures. The 20 normal subjects had a mean RPEP of 0·068 ±0·10 s (range of 0·047 to 0·092 s). The RPEP values of the 9 patients with normal PA mean pressure had a similar range and mean to the normal subjects. Fig. 10 shows that the 19 patients with raised PA mean pressures had a mean RPEP of 0·098 ±0·021 s (range 0·059 to 0·141 s). RPEP was significantly longer than in normals ($P < 0{\cdot}001$). The 4 longest RPEP values were in the patients with atrial fibrillation. None of the normal subjects had RPEP values of 0·095 s or greater whereas 10 of 19 (53%) patients with pulmonary hypertension had such values. Thus, a RPEP of greater than 0·095 s had a specificity of 100 per cent for pulmonary hypertension and a sensitivity of 53 per cent. The relation between RPEP and PA end-diastolic pressure was also examined but did not improve the separation between normal subjects and those with pulmonary hypertension.

Normalised RPEP
None of the normal subjects or patients with normal PA mean pressure had normalised RPEP values of 0·095 or greater, while 13 of 19 (68%) of those with pulmonary hypertension did (Fig. 11). Thus, the specificity remained at 100 per cent and the sensitivity improved to 68 per cent. Mean normalised RPEP was also significantly greater in patients with pulmonary hypertension than in normal subjects ($P < 0{\cdot}001$).

Right ventricular ejection time
Right ventricular ejection time (RVET) could be measured in none of the 20 normal subjects and in only 1 of the 9 patients with normal PA mean pressure. RVET was measured in 9 out of 19 (47%)

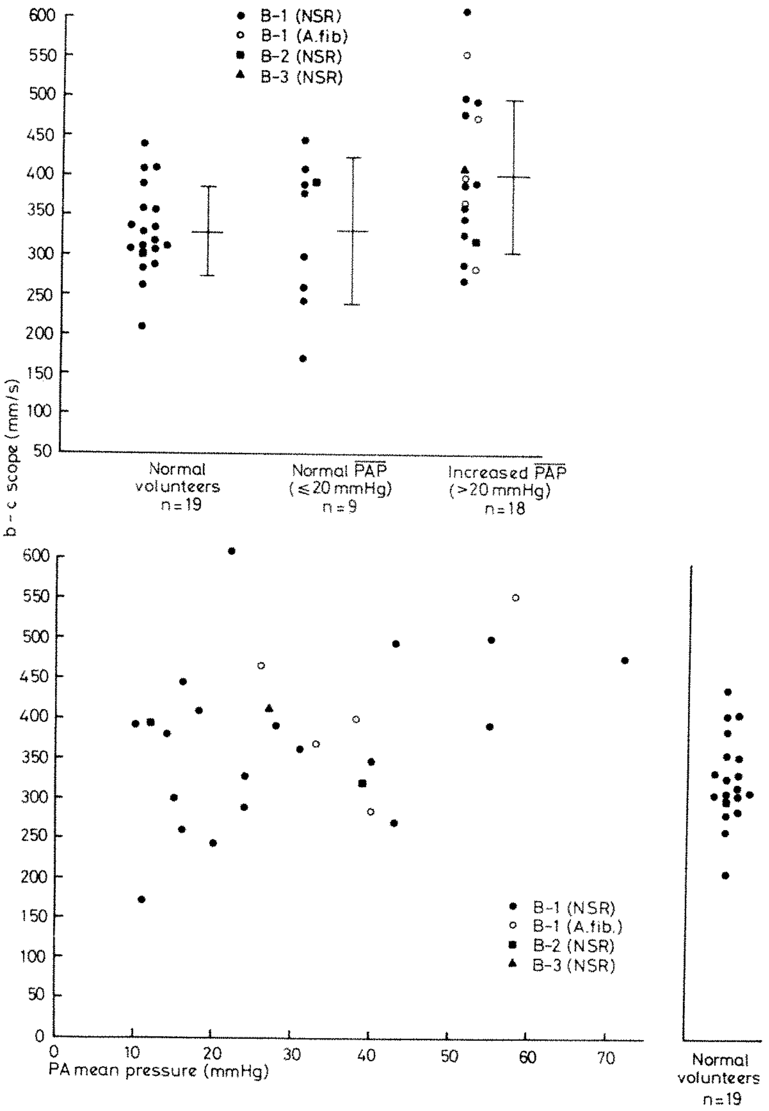


Fig. 8 *Individual b–c slope data. All those with a b–c slope more than 450 mm/s had pulmonary hypertension* (upper panel). *There is a rough correlation between the b–c slope and the level of PA mean pressure, but the scatter is wide. $\overline{PAP}$, pulmonary artery mean pressure; NSR, normal sinus rhythm; A. fib., atrial fibrillation.*

with pulmonary arterial hypertension. Values ranged from 0·207 to 0·432 s (mean 0·315 s) in those with sinus rhythm and from 0·480 to 0·630 s (mean 0·542 s) in those with atrial fibrillation. The ratio RPEP/RVET ranged from 0·14 to 0·45 (mean 0·32) in those in sinus rhythm and exceeded 0·3 in 3 of 5 patients; this ratio ranged from 0·48 to 0·63 (mean 0·54) in 3 patients with atrial fibrillation in whom it could be measured.

Discussion

Variations in pulmonary valve motion in normal subjects indicated to us that a classification of the variations seen in pulmonary valve echo motion in normal subjects was a prerequisite for a definition of the changes found in patients with pulmonary arterial hypertension. To our knowledge there have have been no previously published standard methods of measurement for the various portions of the pulmonary valve echogram.

e–f SLOPE

Of the 4 types of e–f slope (Fig. 1), pattern E-2 includes the previously described anterior e–e′ motion followed by the normal posterior e′–f segment and is believed to reflect transmitted aortic pulsation (Weyman *et al.*, 1974a, b). Recent evidence also indicates that left atrial size and pulsation also may play a role in determining the shape of the e–f slope (Pocoski *et al.*, 1978).

Weyman and colleagues (1974b) also have described a pattern in which the normal posterior e–f motion terminates early and is followed by a short flat segment. They reported that the length of this flat segment was directly related to cycle length and for measurement used the initial rapid e–f slope. In such instances we also measured the predominant rapid slope. However, we found a large variation in the length of the terminal flat segment as compared with the initial rapid posterior motion. In many normal subjects the initial motion was short, rapid, and posterior followed by a long flat slope. Fig. 1 shows an example in which the e–f slope is divided equally between posterior motion in the first half followed by flat motion in the second half (pattern E-3). This common variation occurred in 30 per cent (6/20) of our normal subjects. When the flat motion predominated in this group, it was used for measurement of the e–f slope.

In pattern E-4 an incomplete e–f slope was recorded. This variation could easily represent the terminal portion of any of the other patterns. Because many pulmonary valve echo recordings are incomplete, we advocate routine measurement of the terminal motion of all e–f slopes because this would represent the most consistently reproducible slope. For example, if the initial posterior motion is measured as in pattern E-3, subsequent echo recordings may only include the terminal portion, invalidating any comparisons.

Weyman and colleagues (1974b) reported that

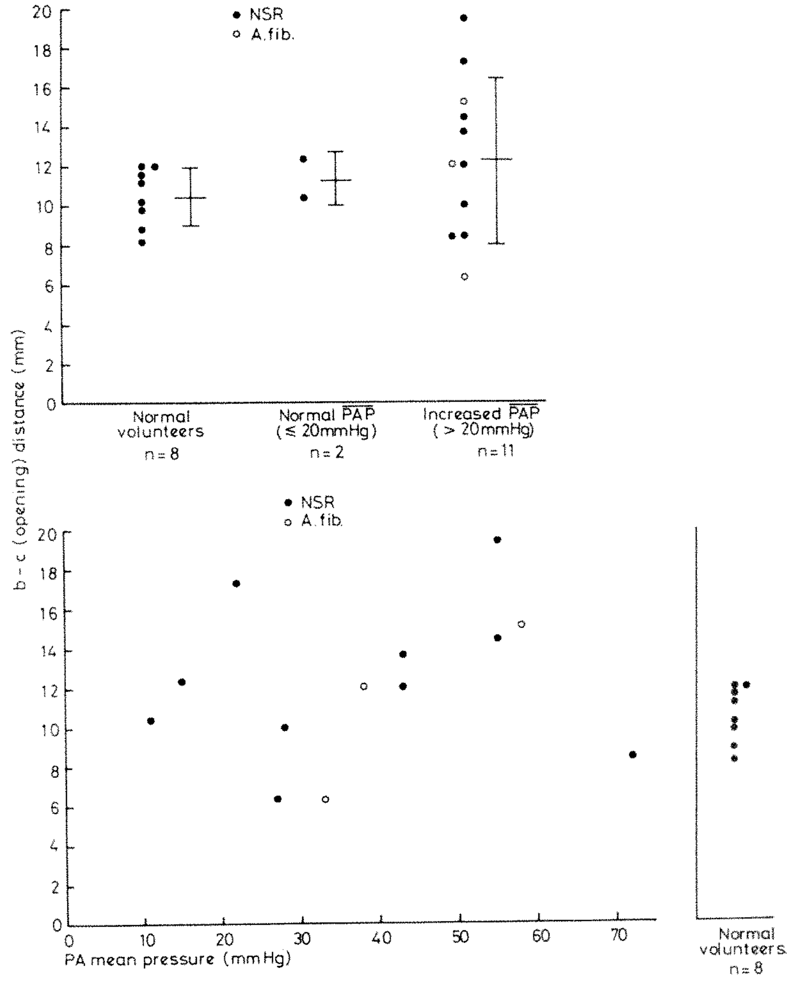


Fig. 9 *Individual data for b–c opening distance. This measurement could not be made in many patients and normal subjects. PAP, pulmonary artery mean pressure; NSR, normal sinus rhythm; A. fib., atrial fibrillation.*

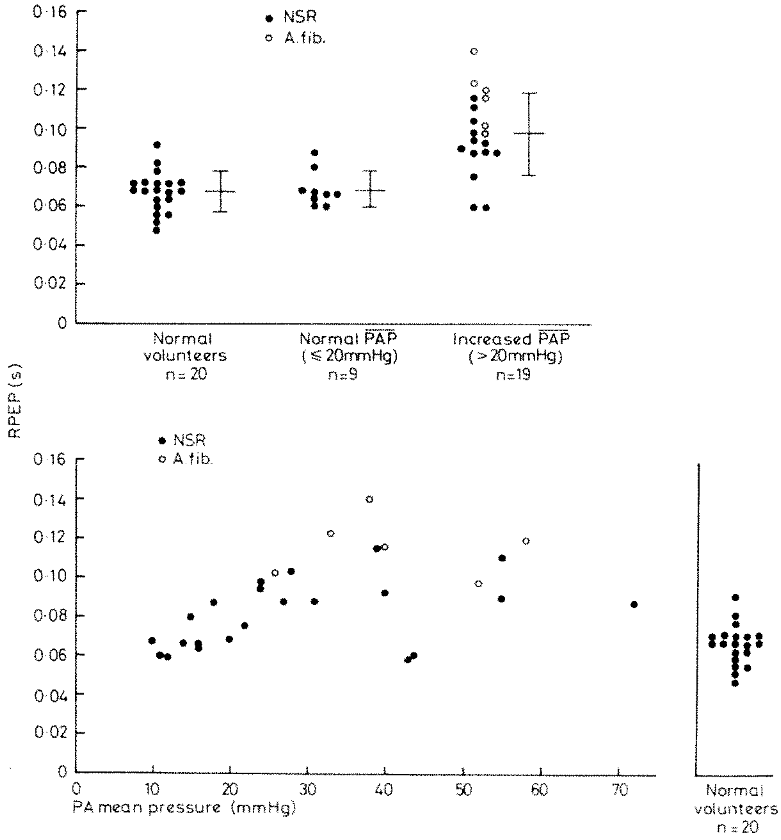


Fig. 10 *Data for right ventricular pre-ejection period (RPEP). All patients with RPEP more than 0·095 have pulmonary hypertension* (upper panel). *Nevertheless, many patients with increased mean pulmonary artery pressure have normal values* (upper and lower panels). $\overline{PAP}$, *pulmonary artery mean pressure; NSR, normal sinus rhythm; A. fib., atrial fibrillation.*

patients with pulmonary hypertension tended to have flat e–f slopes but the overlap with normal subjects limited the usefulness of this measurement. However, they reported that negative e–f slopes, present in 6 of 32 patients but none of their normal subjects, were specific for pulmonary hypertension. Our data suggest that the overlap between e–f slopes in normal subjects and in patients with pulmonary hypertension is too great to be of any value. Moreover, negative slopes were found in 4 of 27 (15%) normal subjects and patients with normal PA mean pressure but in only 1 of 18 (6%) with pulmonary arterial hypertension.

a DIP

In normal subjects deep inspiratory a dips, in which the pulmonary valve opens from a partially open or domed position, have been described (Weyman *et al.*, 1974a). This phenomenon occurs especially in the presence of a short PR interval, but the normal anterior motion to the b point is seen again during expiration. However, in 4 of our 20 normal subjects the posterior leaflet of the pulmonary valve never moved anteriorly following the trough of the a dip. In these subjects, the pulmonary valve opening began from a position at approximately the same level as the trough of the a dip. This occurred throughout the tracing, even during expiration and with a normal PR interval. In this group (pattern A-3) measurement of the a wave excursion was from f point to plateau of the a dip.

Several investigators have reported that an A_{max} of 2 mm or less is useful in separating patients with normal from those with raised PA mean pressure (Nanda *et al.*, 1974; Weyman *et al.*, 1974a, b; Kaku *et al.*, 1978). A greater frequency of absent a dips has been reported at higher PA mean pressures (Nanda *et al.*, 1974). Our data are in agreement with the hypothesis that A_{max} values are very useful in separating patients with pulmonary arterial hypertension from those with normal PA pressures. We found that when A_{max} of less than 2 mm was used as a criterion of pulmonary hypertension (PA mean pressure more than 20 mmHg), specificity was 100 per cent and sensitivity 69 per cent. The sensitivity was improved to 90 per cent when only patients with PA mean pressure exceeding 25 mmHg were considered.

It is believed that the a dip represents opening or doming of the pulmonary valve in response to the transmitted pressure rise from right atrial contraction. In pulmonary arterial hypertension there is a raised pressure distal to the pulmonary valve that prevents or reduces the opening motion after atrial contraction. However, some patients with pulmonary hypertension may have misleadingly high A_{max} values, greater than 2 mm, in the presence of right ventricular failure. One explanation for this phenomenon is that the raised right ventricular end-diastolic pressure reduces the effective diastolic gradient across the pulmonary valve, thus allowing movement (often more than 2 mm) despite the raised PA mean pressure. Such an inverse relation was found in our data. Patients with pulmonary arterial-right ventricular end-diastolic pressure gradients of 10 mmHg or more tended to have smaller A_{max} values than patients with an end-diastolic gradient across the pulmonary valve of less than 10 mmHg. Of the 6 patients with pulmonary arterial hypertension who had an identifiable a dip, 4 had a raised right ventricular end-diastolic pressure with reduced pulmonary arterial-right ventricular end-diastolic pressure gradient.

b–c SLOPE

Nanda and associates (1974) reported that the b–c slope was less steep in normal subjects than in patients with pulmonary hypertension. By contrast, Kerber and Maximov (1976) showed in dogs that the b–c slope failed to increase with an acute increase in mean pulmonary arterial pressure. Kaku *et al.* (1978) found that the b–c slope did not help to identify patients with pulmonary hypertension. Our data suggest that patients with pulmonary hypertension do have steeper b–c slopes than normals ($P = 0{\cdot}006$) but there is great overlap. When used as a criterion for pulmonary hypertension, a very rapid slope of 450 mm/s or more was found to be 100 per cent specific but sensitivity was only 33 per cent. The more rapid b–c slope in some of these patients may be explained by prolongation of the

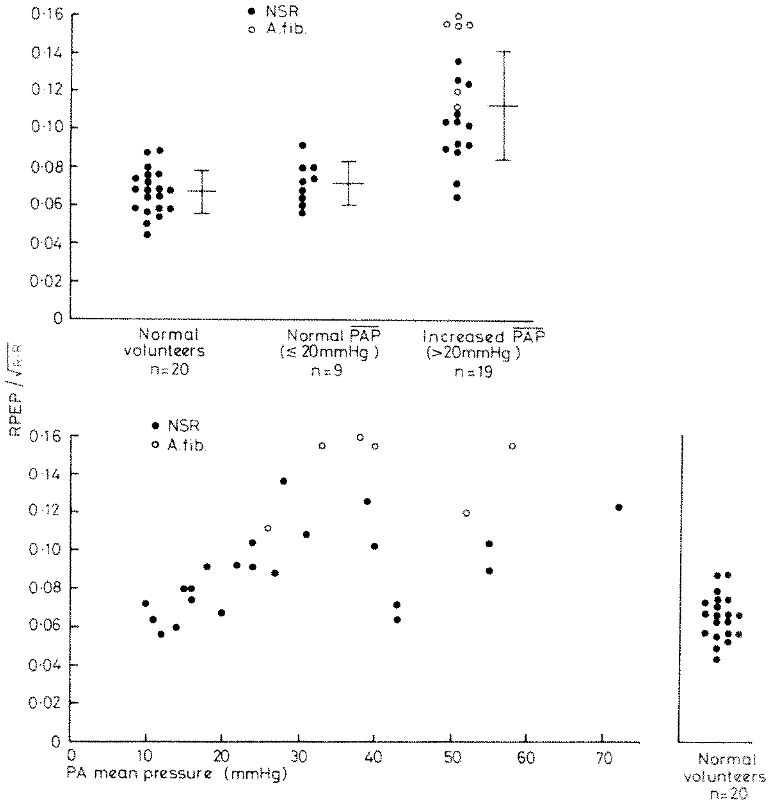


Fig. 11 *Right ventricular pre-ejection period corrected for heart rate (RPEP/√R-R). This is little better than RPEP alone for identifying patients with pulmonary hypertension, but is somewhat more sensitive. $\overline{PAP}$, pulmonary artery mean pressure; NSR, normal sinus rhythm; A. fib., atrial fibrillation.*

right ventricular pre-ejection period (see below). Under these conditions pulmonary valve opening occurs later, at a time when right ventricular dP/dt is higher, thereby leading to the more rapid opening of the pulmonary valve.

b–c OPENING AMPLITUDE

The pulmonary valve b–c opening amplitude in pulmonary hypertension was examined by Weyman *et al.* (1974b), who found no significant difference from normal, and by Nanda *et al.* (1974) who found that normal subjects had significantly smaller amplitudes (Nanda *et al.*, 1974). The b–c opening amplitude was measurable in fewer than half of all our normal subjects and patients. The overlap was considerable with no significant difference in mean opening amplitude between the 2 groups. However, none of the normal subjects had b–c opening amplitudes of greater than 13 mm as compared with 5 of 11 (45%) patients with raised PA mean pressures. Thus, a b–c opening amplitude more than 13 mm was by itself a useful criterion with 100 per cent specificity and 45 per cent sensitivity. Though a rapid b–c slope might be expected to occur in pulmonary stenosis, such an abnormality has not been described (Weyman *et al.*, 1974a). Further, in the presence of sinus rhythm, the amplitude of the a dip would distinguish pulmonary hypertension from pulmonary stenosis. The b–c opening amplitude is probably related to the anatomical size of the pulmonary artery and an increased value should therefore be related to radiographic evidence of an enlarged pulmonary artery.

MIDSYSTOLIC NOTCHING

Midsystolic notching of the pulmonary valve produces a ‘W’ configuration during systole and has been reported only in patients with pulmonary hypertension (Sakamoto *et al.*, 1974; Weyman *et al.*, 1974b). We also found this pattern to be very specific (100%) for pulmonary hypertension.

The sensitivity of this sign in patients with sinus rhythm was 38 per cent (5/13). It occurred in all 4 of the patients with the highest PA mean pressure and in the 4 patients with the highest PA systolic pressures (74 to 104 mmHg). The genesis of this abnormality is unknown. It has been shown by Sakamoto *et al.* (1974) in patients with pulmonary hypertension and pulmonary systolic murmurs that the end of the murmur coincides with the peak of the midsystolic notch (the tip of the centre of the ‘W’). They also observed a systolic click occasionally occurring at the same time, believed to result from the sudden checking of pulmonary cusp motion.

RIGHT VENTRICULAR SYSTOLIC TIME INTERVALS

Nanda *et al.* (1974) reported that the right ventricular pre-ejection period (corrected for heart rate) was prolonged in the presence of pulmonary hypertension. Hirschfeld *et al.* (1975) found that both the right ventricular pre-ejection period and the right ventricular ejection time shortened with increasing heart rates and with decreasing age in their paediatric population. They reported that the ratio RPEP/RVET was independent of heart rate and age and correlated well with the PA diastolic and mean pressures and with the pulmonary vascular resistance. As the ratio increased so did the percentage of patients with PA diastolic pressures greater than 25 mmHg. Mills *et al.* (1975) measured the time between tricuspid valve closure and pulmonary valve opening by echocardiography (right ventricular isovolumic contraction time) and reported prolongation of this interval in patients with raised PA end-diastolic pressure.

In our study right ventricular pre-ejection period was useful in identifying patients with pulmonary hypertension. This measurement was especially helpful because it could be recorded in all 48 of the echocardiograms analysed. A right ventricular pre-ejection period of more than 0·095 s was found in none of the normals but occurred in 10 of 19 (53%) with pulmonary hypertension. As an ultrasound criterion for pulmonary hypertension, RPEP had 100 per cent specificity and 53 per cent sensitivity. Right ventricular pre-ejection period normalised for heart rate also had a 100 per cent specificity and improved sensitivity (68%).

Right ventricular ejection time could not be measured in any of the normal subjects or patients with normal PA mean pressure. It could be measured in only 47 per cent (9/19) of those with pulmonary hypertension. Though values were obtained for the ratio of right ventricular pre-ejection period to right ventricular ejection time, the inability to measure the latter in all normal subjects and in many patients reduced its usefulness in the identification of pulmonary hypertension.

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Obstruction of superior vena caval pathway after Mustard's repair[1]

Reliable diagnosis by transcutaneous Doppler ultrasound

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SUMMARY Superior vena caval pathway obstruction is an important cause of late morbidity and mortality after Mustard's operation. Clinical detection of such obstruction is frequently difficult because of the development of an extensive collateral venous circulation which decompresses the superior vena cava.

As flow is less likely to be normal than pressure, we recorded jugular venous flow profiles transcutaneously in 34 patients after Mustard's operation for simple transposition using a bidirectional Döppler blood velocimeter. There was an independent diagnosis by catheterisation in 14 cases, 4 of whom were restudied after revision of obstruction. Most patients showed a dominant forward flow peak during ventricular diastole and none of these showed any clinical evidence of pathway obstruction. This pattern was considered normal after a Mustard repair, particularly as it was also seen in 4 patients immediately after a revision operation. The jugular flow profile is not the same as in children without heart disease, presumably because of the anatomical differences and the reduction in atrial compliance produced by Mustard's operation. Jugular venous flow in patients even with mild superior vena caval pathway obstruction differed from that in the unobstructed group by exhibiting either non-pulsatility or, more commonly, a dominant forward flow peak in ventricular systole. This quick, simple, and convenient test proved to be diagnostic of the presence or absence of obstruction and, as many patients are asymptomatic, is now the most effective way of screening for this complication. It may thus make catheterisation unnecessary.

Superior vena caval pathway obstruction is an important cause of late morbidity and mortality after Mustard's operation (Mustard, 1964) for the physiological correction of complete transposition of the great arteries (Macartney *et al.*, 1979). The incidence is related to the material and shape of the patch (Stark *et al.*, 1974). The obstruction is not within the superior vena cava itself, but is within the superior vena caval pathway created in forming a new systemic venous atrium during the operation (Fig. 1), and is either upstream or downstream of the right atrial appendage. This has interesting and important effects on the clinical presentation of superior vena caval pathway obstruction, because the haemodynamic effects are different from those of the more familiar superior vena caval obstruction, which occurs within the cava itself. Whatever process occludes the superior vena cava usually occludes the azygos vein as well. By contrast, in caval pathway obstruction, the superior vena cava and azygos vein are wide open. An extensive collateral circulation therefore develops through a dilated azygos and lumbar venous system, allowing superior vena caval blood to return to the heart through the inferior vena cava (Fig. 1) (Stark *et al.*, 1972, 1974; Silove and Taylor, 1976).

Thus complete superior vena caval pathway obstruction can occur without any clinical signs if the collateral venous and inferior vena caval pathways are unobstructed. Though jugular venous engorgement and facial oedema may appear before the development of a collateral venous circulation, they are usually late signs indicating obstruction of

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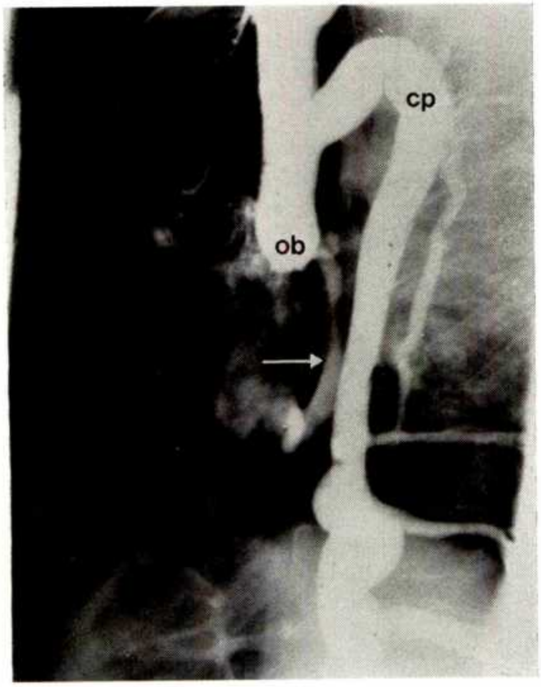

Fig. 1 *Superior vena caval angiogram showing post-Mustard obstruction (ob) with drainage through a collateral pathway (cp), blood eventually returning via the inferior vena cava. The vessel just posterior to the heart* (white arrow) *is the coronary sinus which was opacified from a left superior vena cava.*

both the inferior and superior vena caval pathways. The need for a method of detection of pathway obstruction before the development of clinical signs is obvious. Previous studies have concentrated on patients who are symptomatic by virtue of a raised superior vena caval pressure (Stark *et al.*, 1972, 1974; Venables *et al.*, 1974; Silove and Taylor, 1976). However, when asymptomatic patients are routinely investigated after Mustard's operation, our own experience and that of others (Hagler *et al.*, 1978) shows that severe, even complete, superior vena caval pathway obstruction may be found angiocardiographically, even when there is only a very small pressure gradient between the superior vena cava and systemic venous atrium, presumably because of a large collateral flow. This is consistent with the finding that such patients do not necessarily have a raised or abnormal jugular venous pressure and pulse.

Our hypothesis was that flow is less likely to be normal than pressure and that detection of superior vena caval pathway obstruction might therefore be possible non-invasively using a transcutaneous Döppler ultrasound bidirectional blood velocity probe. If this were so, use of this method would have the added advantage that it might obviate the need for confirmation of the diagnosis by cardiac catheterisation, which is not only time-consuming, expensive, and unpleasant for the patient, but may also present a real problem of access to veins which tend to become thrombosed either because of previous catheterisations or because of polycythaemia before Mustard's operation.

Methods

Jugular venous flow velocity recordings were made in 34 patients (age range 0·4 to 17·2 years, mean 6·8 years), all of whom had previously had a Mustard's repair for simple complete transposition of the great arteries between 1 week and 12·3 years (mean 5·0 years) before investigation. Four patients were studied before and after revision of obstruction giving a total of 38 recordings. The baffle was fashioned from pericardium in 23 and from Dacron in the remainder. Recordings were made either routinely at an outpatient clinic or when patients were admitted for cardiac catheterisation or revision of Mustard's operation. A transcutaneous bidirectional Döppler ultrasound blood velocimeter[1] was used, which incorporated an electrocardiogram and flow channel, plotting both directly onto an integral paper chart recorder. The machine also emits an audible tone whose frequency is proportional to the velocity signal. The transmitter frequency was 7·52 MHz.

Patients were quiet and supine with no pillow and the head was turned slightly away from the examination. The limb leads of the electrocardiograph were attached to the patient and the instrument checked for an appropriate electrocardiographic deflection (demonstrating the P waves in particular) on the recording paper. The external probe was applied to the skin using Aquasonic 100 ultrasound transmission gel[2]. The probe was placed over the jugular vein and directed toward the inferior border of the contralateral scapula. Its position was then adjusted until the signal reached a maximum as determined both by ear and by looking at the display on a Sonicaid BV 383 memory oscilloscope. When this signal was consistent, reproducible, and pure, free from components of flow from adjacent arteries, the electrocardiogram and jugular flow signals were then recorded simultaneously on the chart recorder at a paper speed of 50 mm/s using a foot-switch control. Recordings were obtained from both left and right jugular veins, after which a carotid

[1] Sonicaid Ltd., England. Model BV381.
[2] Parker Laboratories, New Jersey.

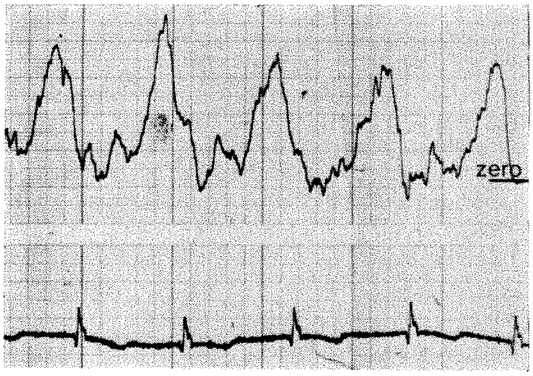

Fig. 2 *Jugular venous flow recording after Mustard's operation with no superior vena caval pathway obstruction. Dominant forward flow occurs during ventricular diastole.*

recording was also made to verify that there was no arterial component in the venous flow records. Zero flow was recorded routinely as a reference level and both venous and arterial forward flows were displayed as positive deflections by the appropriate use of the reversal switch, standard to this instrument.

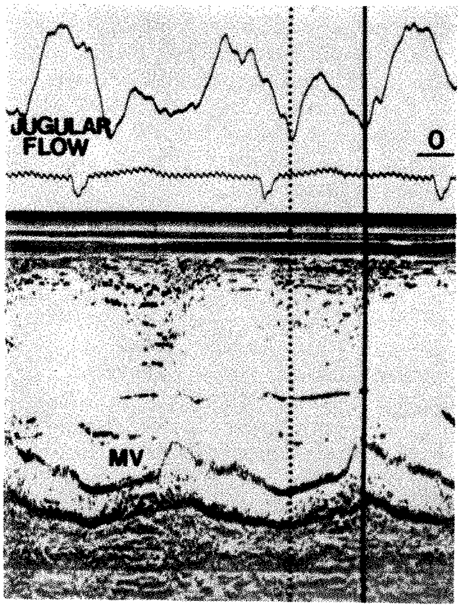

Fig. 3 *Simultaneous echocardiogram* (below), *electrocardiogram* (middle), *and jugular flow recording* (above) *in a patient with no superior vena caval pathway obstruction. Systolic forward flow begins just after the left ventricular posterior wall starts to move forward* (dotted line). *Diastolic forward flow begins just after mitral valve opening* (solid line). *Paper speed 50 mm/s.*

The timing of mitral valve movement was compared with the jugular flow profile in 4 patients by feeding Döppler, electrocardiographic, and echocardiographic[1] signals directly to a Cambridge fibre-optic physiological recorder[2] with echoscan converter, and recording these signals onto the integral ultraviolet paper output.

At cardiac catheterisation, criteria for the diagnosis of superior caval obstruction were a superior vena caval pathway of less than half the diameter of the superior vena cava in the frontal view of the superior vena caval angiogram, the passage of a significant amount of contrast medium from superior to inferior caval territory via the azygos system, and a mean pressure gradient of more than 4 mmHg between superior vena cava and systemic venous atrium (Silove and Taylor, 1976).

Results

Thirty-four patients (89%) had recordings similar to that shown in Fig. 2 in that the dominant forward flow peak occurred during ventricular diastole. Four of these were obtained when the pathway was known to be unobstructed after revision of superior vena caval pathway obstruction. Six more patients in this group had had previous cardiac catheterisation studies in which the superior vena caval pathway was shown to be unobstructed. The jugular venous wave pattern seen in these patients was taken to be that associated with a normal wide unobstructed superior vena caval pathway. This waveform is characterised by a large forward flow in ventricular diastole with less flow in ventricular systole (Fig. 2). This increase in forward flow is shown in Fig. 3 to occur only after the mitral valve has opened, further evidence of an unobstructed superior vena caval pathway.

However, in the 4 cases before revision of pathway obstruction and in a further 4 awaiting revision (after confirmation of diagnosis by cardiac catheterisation), flow patterns were significantly different from those in the unobstructed group. In these patients the waveform was either non-pulsatile (Fig. 4a) or, more commonly, showed dominant forward flow during ventricular systole (Fig. 5a). Whatever the waveform before revision it reverted to the same unobstructed pattern after revision (Fig. 4b and 5b). These results are summarised in the Table.

A number of patients showed flow reversal during atrial systole, but this could not be correlated with the presence, absence, or degree of obstruction,

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[1] Ekoline 20, Smith-Kline Instruments Ltd.

[2] Type 01005, Cambridge Medical Ltd., England.

Table *Effect of superior vena caval pathway obstruction (SVCPO) on jugular venous waveform in 18 catheterised or reoperated patients*

		Dominant diastolic wave	*Dominant systolic wave or non-phasic trace*
SVCPO	present	0	8
	absent	10	0

P < 0·001.

the placement of the baffle (particularly its relation to the right atrial appendage), or to the cardiac rhythm.

Discussion

Since Kalmanson *et al.* (1968, 1969) showed that jugular venous flow waveforms detected by transcutaneous Döppler ultrasound were an accurate reflection of the total venous return, the technique has so far found few applications in paediatric cardiology apart from the diagnosis of atrial (Kalmanson *et al.*, 1972) and ventricular (Kalmanson *et al.*, 1974) septal defects and estimation of shunt size, for which other equally reliable non-invasive techniques exist. Kalmanson's results suggest that certain jugular venous waveforms are diagnostic of specific lesions and this view has been endorsed by Sivaciyan and Ranganathan (1978), who established that these waveforms reflect

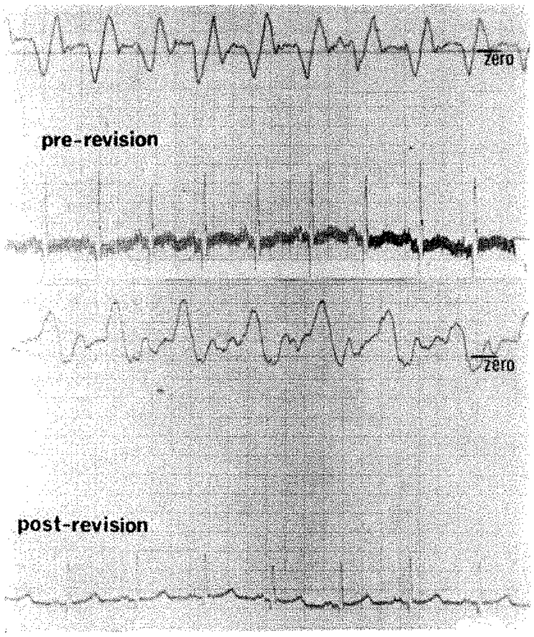

Fig. 5 (a) (above) *Jugular venous flow recording in a patient after Mustard's operation but with severe superior vena caval pathway obstruction. Dominant forward flow occurs in ventricular systole. This was a more common finding than completely non-pulsatile flow.* (b) (below) *After revision of obstruction the dominant wave was in ventricular diastole.*

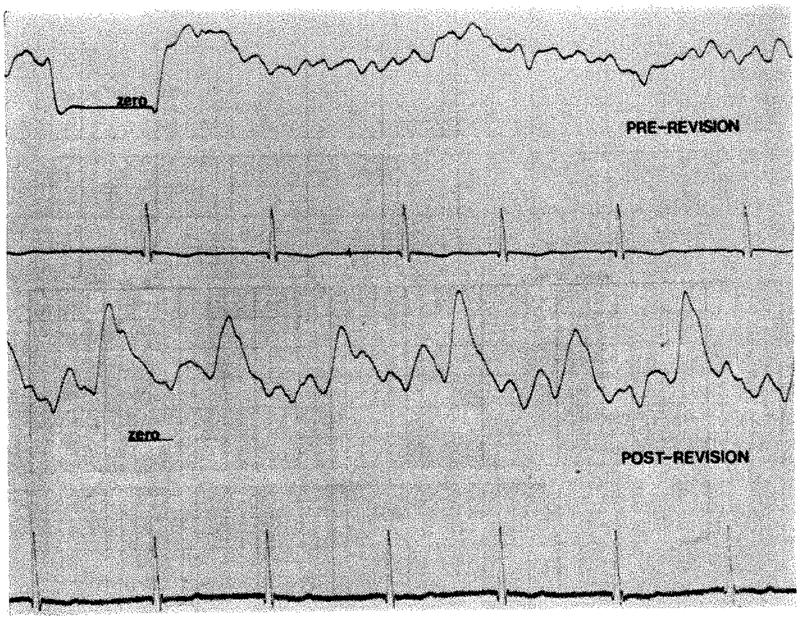

Fig. 4 (a) (above) *Jugular venous flow recording in a patient after Mustard's operation but with severe superior vena caval pathway obstruction. The flow pattern is non-pulsatile.* (b) (below) *The recording in the same patient after surgical revision of obstruction now shows dominant forward flow in ventricular diastole.*

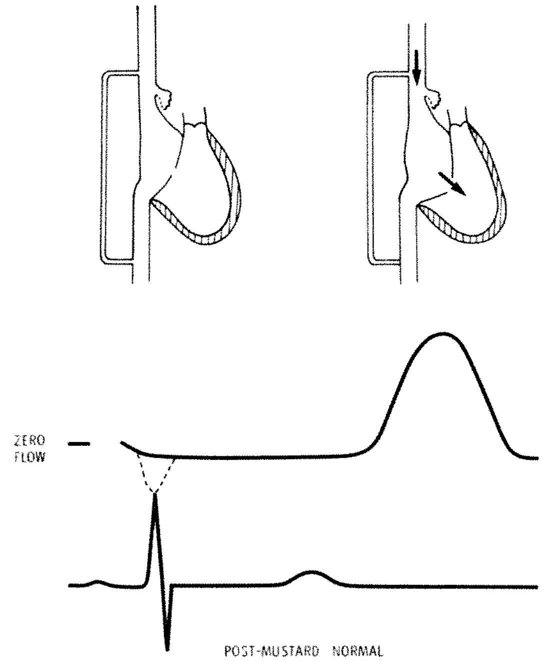

Fig. 6 *With an unobstructed superior vena caval pathway, ventricular filling after mitral valve opening was reflected in a dominant jugular forward flow wave during diastole; there was sometimes flow reversal during atrial systole.*

derangements in right heart haemodynamics irrespective of the underlying aetiology.

In the normal heart, the jugular venous flow record shows two maxima of roughly equal size, one during ventricular systole and atrial relaxation, and the other during ventricular diastole. In no post-Mustard case was this so. Even with an unobstructed superior vena caval pathway, forward flow was much greater during ventricular diastole, occurring once the mitral valve had opened. The explanation of the reduced forward flow during ventricular systole may be that the mitral valve descends less than the tricuspid and therefore cannot increase atrial volume to the same extent as in the normal heart. However, if mitral valve movement is to be held responsible for forward flow during ventricular systole, one would expect less flow in the presence of superior vena caval pathway obstruction, whereas exactly the opposite occurs. A more likely explanation is that the reduction of atrial compliance after Mustard's operation negates the effects of atrial relaxation and reduces or completely abolishes atrial filling during ventricular systole. The loss of atrial compliance is reflected in the systemic venous atrial pressure pulse by a steep y-descent (Silove and Taylor, 1976). Such a reduction in atrial compliance might also explain why a few of the jugular venous recordings from post-Mustard patients showed flow reversal during atrial systole. The origin of the diastolic flow peak is depicted diagrammatically in Fig. 6.

How pathway obstruction creates an abnormal jugular venous waveform is depicted in Fig. 7. Because of the obstructed pathway the forward flow peak corresponding to mitral valve opening is lost. Pulsatility may be lost completely when collateral channels are poorly developed or inferior vena caval pathway obstruction also present. However, some patients with severe obstruction of both caval pathways had pulsatile flow nevertheless. Why, in patients with superior vena caval pathway obstruction, the peak of jugular venous forward flow occurs during ventricular systole remains unclear at present. One explanation would be that the jugular flow pattern is out of phase with forward flow through the mitral valve during ventricular diastole, because of the length, volume, and compliance of the collateral venous system. How-

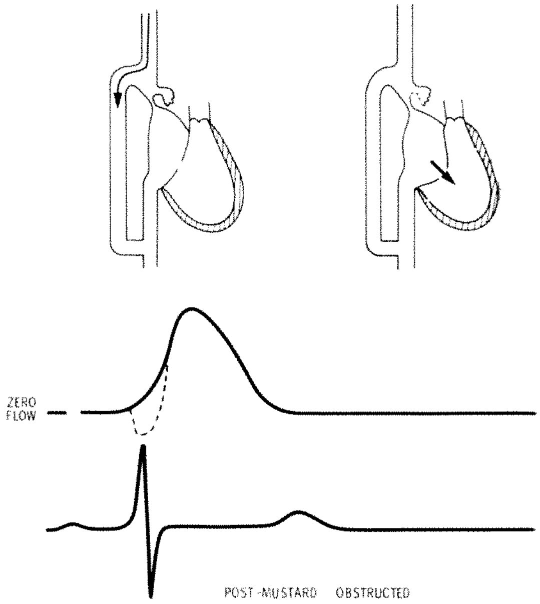

Fig. 7 *With an obstructed superior vena caval pathway, ventricular filling after mitral valve opening does not directly influence the jugular venous flow pattern. Blood flow down the collateral pathway probably occurs mainly during ventricular systole giving rise to the change in phase of dominant jugular forward flow from diastole to systole. There is sometimes flow reversal during atrial systole.*

ever, if this were the explanation, it is surprising that the timing with ventricular systole is so exact. An alternative explanation is that motion of the heart during systole exerts traction on the superior vena cava in such a way as to encourage forward flow. Nevertheless, whatever the mechanism involved, the resultant pattern of jugular venous flow is so obviously different from that in unobstructed patients as to make the technique reliably diagnostic of superior vena caval pathway obstruction. Further, it has been shown to detect even mild and asymptomatic total obstruction which was hitherto impossible without cardiac catheterisation, and has done so with no false positive or negative results. The patient population was deliberately biased towards patients with obstruction, so the overall incidence of obstruction is not representative.

The use of Dacron baffles, which were associated with rather rapid progression of obstruction, has been discontinued. Our present policy in patients with pericardial baffles is not to operate unless both superior and inferior vena caval pathways are obstructed, since experience has shown that even complete obstruction of one pathway is well tolerated for many years provided the other pathway is clear, because of the collateral circulation. This means that though an asymptomatic postoperative patient with a normal jugular flow trace does not require cardiac catheterisation to exclude caval pathway obstruction, an asymptomatic patient with an abnormal jugular venous flow trace does require catheterisation not to detect superior vena caval pathway obstruction, but to assess its severity and ensure that the inferior vena caval pathway is clear. In a patient with facial oedema and jugular venous engorgement, a jugular venous flow recording denoting obstruction has already been used as an indication for revision of the Mustard operation without further cardiac catheterisation. As the technique also provides an early diagnosis of impending superior vena caval obstruction, the information thus obtained can be used to assess the effects of modifications of surgical technique which attempt to reduce the incidence of caval pathway obstruction. The study is now being extended to patients with complex transposition, and also to assessment of the inferior vena caval pathway.

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Non-invasive pulsed Doppler study of mitral stenosis and mitral regurgitation: preliminary study

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SUMMARY The potential value of pulsed Doppler echocardiography in the evaluation of mitral valve lesions was studied before cardiac catheterisation in 64 patients with a clinical diagnosis of mitral valve disease. Mitral stenosis was evaluated with the transducer sited at the apex and oriented towards the mitral orifice. Reproducible tracings were obtained when a mitral flow running towards the transducer was recorded when the Doppler sample volume was located close to the mitral annulus and when the flow curves ending with the QRS complex of the electrocardiogram were retained for analysis. Of 37 patients in sinus rhythm, the 14 without a mitral valve gradient had a bifid diastolic flow pattern. In patients with mitral valve stenosis, 3 distinct flow patterns corresponding to significantly different mitral valve gradients were defined. In the presence of atrial fibrillation the Doppler analysis could not differentiate patients with mild mitral stenosis from those without a mitral valve gradient. With moderate and severe stenosis, however, the flow curves were similar to those in sinus rhythm and the method was reliable.

Mitral regurgitation was studied by 2 methods. The first was previously described for the study of mitral stenosis and was later discarded because of low specificity and sensitivity. Use of a parasternal approach improved the performance and the Doppler results were in good agreement with the left ventriculogram when significant mitral regurgitation was present. Thus, these preliminary results suggest that pulsed Doppler echocardiography may be useful as a clinical adjunct for assessing the presence and severity of mitral valve disease.

M-mode echocardiography is frequently used for studying normal and abnormal mitral valve motion. Its usefulness and limitations have been well defined (Feigenbaum, 1976). Bidimensional echocardiography allows a more complete delineation of structures and is currently under study (Henry *et al.*, 1975). Pulsed Doppler echocardiography permits the study of blood flow velocities and profiles (Péronneau and Léger, 1969; Baker, 1970) and, therefore, may be better suited to the investigation of dynamic function. The potential value of this non-invasive approach for evaluating mitral valve stenosis and regurgitation was assessed in this study by correlating the Doppler flow signals to haemodynamic data.

Methods

I: DOPPLER PRINCIPLE AND INSTRUMENTATION

The directional range-gated pulsed Doppler instrument used in this study was a prototype developed by ERA, CNRS 07-785, France. An improved unit is now commercially available (Alvar Electronic). According to the Doppler principle, ultrasound waves are backscattered with a shifted frequency by moving erythrocytes. The difference in frequency is called the Doppler shift and is proportional to the velocity of the target erythrocytes and to the angle between the emitted ultrasound beam and the direction of moving blood cells. When the angle is close to zero, the Doppler shift of frequency is maximal; this frequency shift decreases progressively as the angle moves towards 90° where it becomes absent. With a wider angle the flow curve

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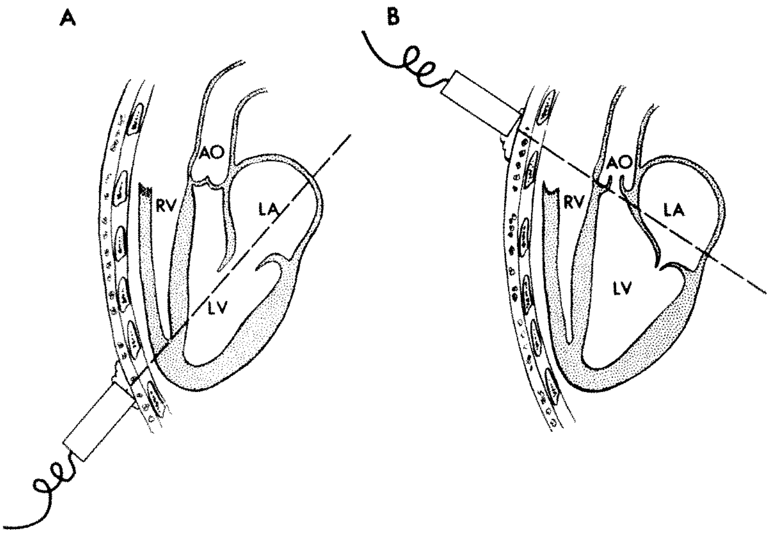

Fig. 1 *Schematic diagrams illustrating the methods of examination. In panel* A, *the transducer is positioned at the apex and oriented towards the mitral valve in the axis of mitral valve flow. The angle between the ultrasound beam and the blood flow is close to zero and the Doppler shift is near maximal. In panel* B, *the transducer is located in the parasternal position and the left atrium is explored by moving the sample volume above and behind the mitral annulus. The apical approach was used in the study of mitral valve stenosis. For mitral valve regurgitation the parasternal approach gave the best results. The dotted line indicates the beam of ultrasound. The sample volume can be sited anywhere along this beam. RV, right ventricle; Ao, aorta; LA, left atrium; LV, left ventricle.*

becomes inverted. The analogue curve of velocity was derived from a zero crossing detector and transcribed on a Gould strip-chart recorder model 2400 along with the electrocardiogram at a paper speed of 25 and 50 mm/s. Zero baseline flow was determined electronically. By convention, the flow curve was recorded as positive when the flow was running towards the transducer and as negative when it was running away from the transducer. In the present study we did not measure the angle between the ultrasound beam and the blood stream and did not attempt a quantification of flow.

The unit has a range-gated system which is adjustable in depth and in width. It transmits at a frequency of 4 MHz and at a pulse repetition rate adjustable from 5 to 20 kHz. The duration of the acoustic pulse generated by the piezoelectric crystal varies from 2 to 4 μs. After a delay, the crystal is allowed to receive for 100 μs or more. The depth at which the velocity is detected is controlled by the duration of the delay in the receiver. It can be set from 3 to 15 cm depending on the pulse repetition rate, a lower pulse repetition rate being necessary for increasing depth. At the same time the pulse repetition rate has to be at least twice the expected Doppler shift. The value of the velocity measured is the average of all the velocities present in the sample volume. A high-pass filter with a cut-off frequency of 500 Hz eliminates low frequencies from cardiac and vessel wall motion. The site of the sample volume is displayed on the simultaneous M-mode echocardiogram and therefore can be exactly located and selected. This property of the pulsed Doppler technique allows a discrimination in depth and an estimation of the width of the flow.

II: MATERIAL, METHODS, AND PATTERNS OF MITRAL VALVE FLOW

The 64 patients included in this study were referred for cardiac catheterisation because of suspected mitral valve disease and were selected on the basis of good-quality M-mode echocardiographic recordings. Fifty patients had rheumatic heart disease, 4 atherosclerotic heart disease, 5 mitral valve prolapse, and 5 cardiac disease of undetermined aetiology. Mean age was 47 years with a range of 19 to 68. The Doppler study was done on the day before cardiac catheterisation. Routine right and left heart catheterisation was performed in the fasting state under local anaesthesia after premedication with diazepam 10 mg per os. Pulmonary wedge pressure and left ventricular pressures were obtained via 8F catheters connected to P23 Db Statham strain gauge transducers. They were recorded simultaneously on a Honeywell fibreoptic strip-chart recorder at paper speed 100 mm/s and at a gain of 4 mmHg/cm. Cardiac output was obtained by the Fick or the dye dilution curve method. Mean mitral valve gradient was measured by planimetry of 5 of 10 cardiac cycles. After pressure recordings, a left ventriculogram was obtained in the 30° or 45° right anterior oblique position. The regurgitant flow was semiquantified into 4 grades (McLaughlin and Morch, 1971); grade 0 = absence of regurgitation when no contrast material entered the left atrium; grade 1 = small puffs of contrast material passed into the left atrium, but in a volume insufficient to opacify the chamber completely; grade 2 = the volume of contrast material entering the left atrium gradually built up to produce complete opacification; grade 3 = complete opacification of the left atrium occurred in the first few cycles after injection of contrast material.

Sensitivity was calculated as the percentage of mitral lesions correctly detected by the Doppler analysis and specificity as the percentage of normal mitral valves correctly diagnosed.

Statistical analysis for mitral stenosis was performed by the Student's t test. The Fisher exact probability test was used to compare the groups with mitral regurgitation.

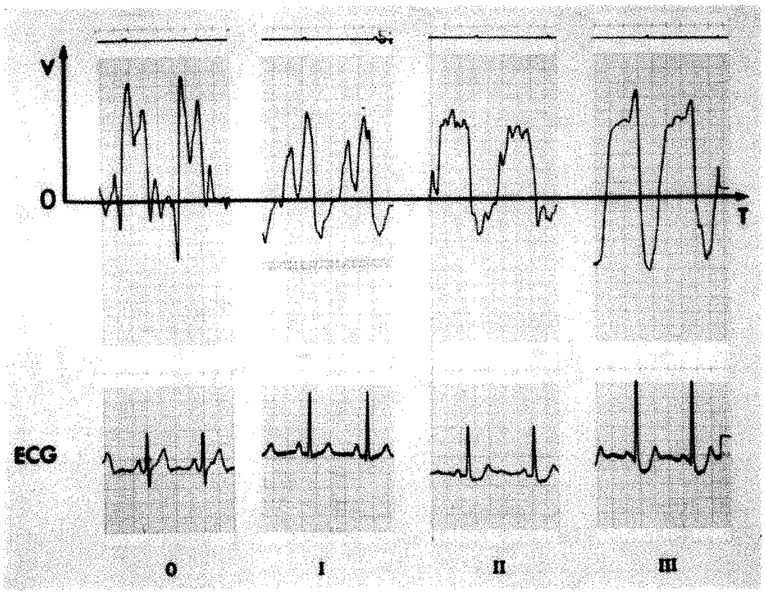

Fig. 2 *Illustrative examples of mitral valve flow recordings in patients with sinus rhythm. The transducer was positioned at the apex and oriented towards the mitral valve. Four recordings are shown corresponding to the Doppler classification of mitral stenosis used in this study. Pattern 0 is a normal bifid flow and was not associated with a mitral valve gradient. Pattern I is also a two-peaked flow but with a relative increase in the amplitude of the late diastolic peak. Pattern II is a single-peaked flow curve, dome-shaped in appearance. Pattern III shows an ascending limb followed by a slight ascending plateau and a sharp decrease towards baseline at the time of the QRS complex. The examples show the recording of a negative flow during systole. This is particularly clear in pattern III. This negative flow represents a flow running away from the transducer and might originate from a regurgitant flow through the mitral valve. However, problems exist for the identification of mitral regurgitation when the transducer is located at the apex. As discussed in the text, this flow might also correspond to the ejection flow in the left ventricular outflow tract during systole. Thus, it is not specific for mitral regurgitation. V, velocity of flow; 0, zero flow baseline; ECG, electrocardiogram.*

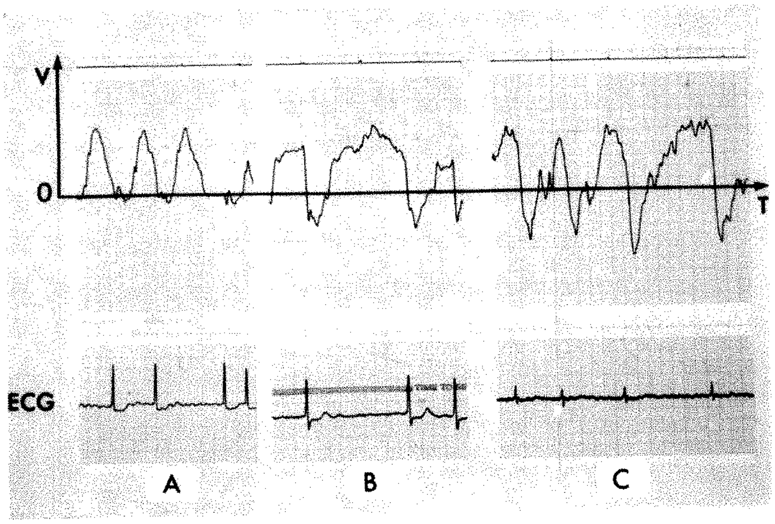

Fig. 3 *Recordings of mitral valve flow in patients with atrial fibrillation. Variation in cardiac cycle length and loss of atrial contraction led to a classification based on the study of long diastoles. Type A shows a flow ending before end-diastole of long cardiac cycles. Type B shows a dome-shaped flow curve and type C a flow with an ascending plateau throughout long diastoles. Abbreviations as in Fig. 2.*

(A) *Doppler analysis of mitral stenosis*

The diastolic mitral valve flow was best recorded when the patients were examined in the left lateral position, the transducer being located at the site of the apical bulge and oriented posteriorly and to the right (Fig. 1A). In this position, flow from the mitral valve was in the axis of the ultrasound beam ±20° and was recorded as positive. The Doppler sample volume was then positioned as close as possible to the mitral annulus. A 5-kHz pulse repetition rate was usually used. Slight adjustment of the angle of the probe and of the sample volume allowed minimisation of noise from the valve leaflets and high-quality flow curve recordings. A good and stable signal was usually recorded when the sample volume was located in the left atrium just behind the anterior leaflet of the mitral valve in its closed position. The Doppler apparatus used in this study introduced a delay of 70 ± 10 ms in its process of analysing the signal. The tracings were reproducible when 3 criteria were met: (1) recording a mitral valve flow running towards the transducer in the axis of the ultrasound beam; (2) the Doppler sample volume was close to the mitral annulus; (3) the flow curves analysed ended with the R wave of the electrocardiogram.

Of the 64 patients, 37 were in sinus rhythm and 27 in atrial fibrillation. In patients with sinus rhythm, 4 characteristic flow patterns could be identified. They are illustrated in Fig. 2. Pattern 0 was a normal smooth flow curve with 2 conspicuous peaks, the first corresponding to rapid filling and occurring in the first third of diastole; the second peak was at the time of atrial contraction and of the A wave of the anterior mitral valve leaflet on the echocardiogram and occurred in the last third of diastole. This flow pattern was similar to the motion of the anterior leaflet of the mitral valve on M-mode echocardiography. Pattern I was similar, but with the late diastolic peak higher than the protodiastolic peak. It was also heard as a turbulent flow. Pattern II was a single-peaked flow with a dome-shaped appearance. A low-amplitude peak of short duration was sometimes observed late in diastole but seemed to represent an artefact related to valve motion.

Pattern III was a flow with a pronounced ascending limb in the first third of diastole followed by an ascending plateau sustained until end-diastole where a sharp descending limb occurred.

In atrial fibrillation, loss of atrial contraction and variations in cardiac cycle length necessitated another classification. This classification was based on the analysis of long diastolic cardiac cycles (Fig. 3). The normal pattern (A) was a flow ending before the QRS complex of the electrocardiogram. Type B was a flow maintained throughout long diastoles, peaking in mid-diastole and thereafter being somewhat dome-shaped. Type C showed a protodiastolic ascending flow followed by a slowly ascending plateau sustained to end-diastole; a sharp descending limb occurred at the time of the QRS complex. Type B in atrial fibrillation resembled pattern II in sinus rhythm and type C in atrial fibrillation resembled pattern III in sinus rhythm.

(B) *Doppler analysis of mitral regurgitation*
Mitral regurgitation was studied in 2 different ways. The first was identical to that used in the study of mitral stenosis. The probe was placed at the apex of the heart and oriented towards the mitral valve (Fig. 1A). In this position, a systolic flow running away from the transducer was sought (Fig. 2). The second approach was similar to the technique used in standard echocardiography. With the patient in the left lateral position, the transducer was placed parasternally in the third or fourth left intercostal space (Fig. 1B). The Doppler sample volume was positioned in the left atrium behind the posterior aortic wall. The mitral valve orifice was explored for a systolic regurgitant flow by slight angulation of the transducer and by moving the electronic sampling gate back and forth (Fig. 4). The first 37 patients were examined by both methods and the last 27 by the parasternal approach only.

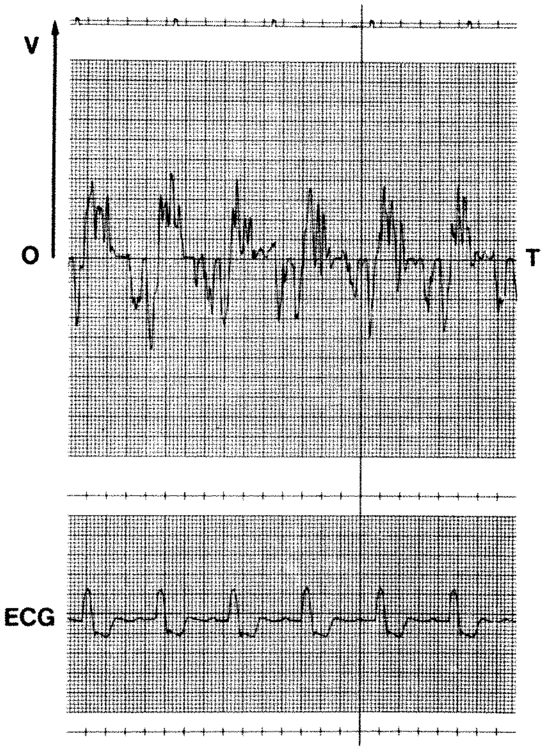

Fig. 4 *Example of recording of mitral regurgitation by the parasternal approach. In this position the sample volume located in the left atrium does not override the inflow and outflow tract of the left ventricle and a systolic ejection flow cannot be recorded. The systolic flow running towards the transducer and recorded as positive represents flow from mitral regurgitation. The normal diastolic two-peaked flow through the mitral valve is also recognised running away from the transducer and recorded as negative. Abbreviations as in Fig. 2.*

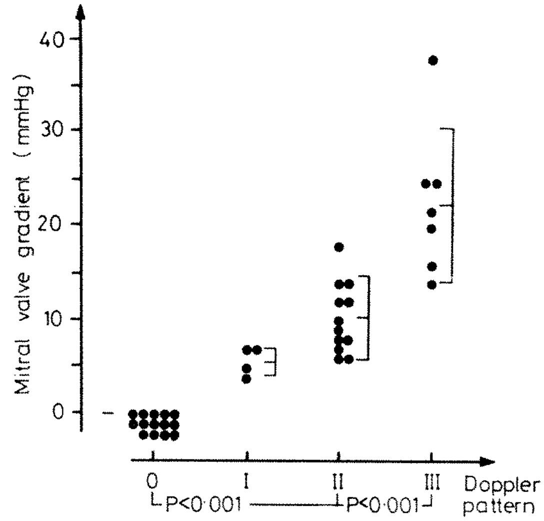

Fig. 5 *The mean mitral valve gradient is plotted against the Doppler flow pattern in patients with sinus rhythm. The Doppler flow pattern could identify all cases of mitral stenosis with no false positives. It also allows semiquantification of the degree of stenosis. The pattern was not altered by the presence or the absence of associated regurgitation.*

Results

I: MITRAL STENOSIS

Correlations between Doppler flow patterns and haemodynamic data are shown in Fig. 5 and 6. Fig. 5 shows the results of 37 patients in sinus rhythm. All 14 patients with a smooth and bifid diastolic flow curve (Doppler pattern 0) had no mitral valve gradient. All patients with Doppler patterns I, II, and III had gradients and the severity of gradient could also be estimated from the flow pattern. In the 4 patients showing Doppler pattern I, the gradient was 5·7 ± 1·5 (SD). Doppler pattern II observed in 12 patients was associated with a mean gradient of 10·3 ± 3·7 and pattern III in 7 patients with a gradient of 22·9 ± 7·9. The difference between groups with patterns 0 and II and with patterns II and III were statistically significant.

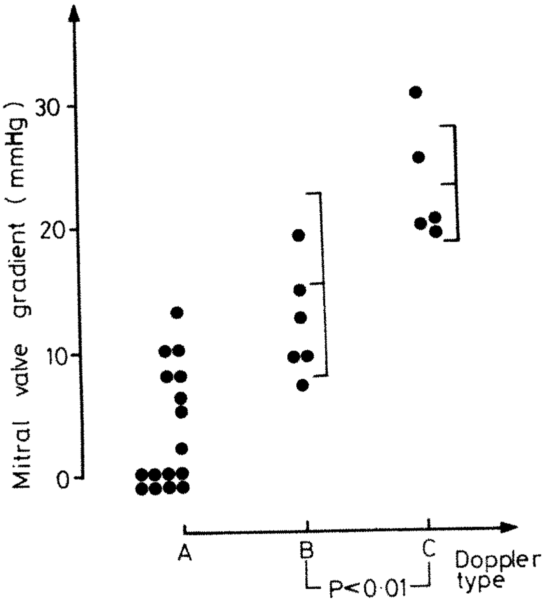

Fig. 6 *Mean gradient plotted against the Doppler type of curve in patients with atrial fibrillation. Types B and C appear specific and allow an appreciation of the severity of mitral stenosis. In type A, the poor sensitivity indicates the actual limitation of this method.*

Fig. 6 shows the results in patients with atrial fibrillation. Half of the 16 patients showing a flow ending before end-diastole (type A) had gradients. A flow with a dome-shaped appearance (type B) or ascending throughout long diastoles (type C) was associated in all patients with gradients (mean of 15 ± 7·6 mmHg and 22·8 ± 4·7, respectively, $P < 0{\cdot}01$).

The mean gradient in Doppler type B in atrial fibrillation was similar to the mean gradient of pattern II in sinus rhythm and the mean gradient of type C was similar to that of pattern III in sinus rhythm. The presence or the absence of associated mitral regurgitation did not alter the results.

II: MITRAL REGURGITATION

Results obtained with both methods of analysis of mitral regurgitation were compared in the first 37 patients and are shown in Table 1. Fig. 2 and 4 illustrate examples of recordings by each method. Of 13 patients without mitral regurgitation on angiography a transmitral systolic flow was recorded by the apical approach in 7 and by the parasternal approach in only 2. Of 14 patients with mild mitral regurgitation (grade 1 on angiography), 2 could be identified by the apical approach and 9 by the parasternal approach. Of the 10 patients with moderate to severe mitral regurgitation (grades 2 and 3), 7 were found by the apical and 9 by the parasternal position. The specificity of the parasternal approach was 85 per cent compared with 46 per cent for the apical approach ($P < 0{\cdot}05$). The sensitivity for the diagnosis of all degrees of mitral regurgitation was 75 per cent for the parasternal approach and 37 per cent for the apical approach ($P < 0{\cdot}01$). For moderate to severe regurgitation, sensitivity was 90 per cent when sampling in the left atrium versus 70 per cent by the apical approach (NS).

Because of its superiority, the parasternal approach was used exclusively in the 27 subsequent patients. As shown in Table 2, of the total of 64 patients, 20 had no angiographic mitral valve regurgitation and the Doppler diagnosis was correct in 18, yielding a specificity of 90 per cent. Overall sensitivity was 59 per cent. Considering only angiographic grade 2 and grade 3 mitral regurgita-

Table 1 *Doppler analysis of mitral regurgitation: comparison of the apical and parasternal approaches*

Regurgitation at left ventriculography		*Number of patients*	*Systolic flow at Doppler analysis*		
			Apical approach		*Parasternal approach*
Grade 0		13	7		2
Grade 1		14	2		9
Grade 2		4	3		3
Grade 3		6	4		6
Sensitivity	All regurgitation		37% ←	P < 0·01	→ 75%
	Regurgitation II and III		70% ←	NS	→ 90%
Specificity			46% ←	P < 0·05	→ 85%

Table 2 *Doppler analysis of mitral regurgitation: parasternal approach*

Doppler	*Ventriculography regurgitation*			
	Grade 0	*Grade 1*	*Grade 2*	*Grade 3*
+	2	11	5	10
–	18	16	1	1

$P < 0{\cdot}0001^*$

Sensitivity: All regurgitation — 59%
Sensitivity: Regurgitation II and III — 88%
Specificity — 90%

+ Indicates the identification of a systolic flow in the left atrium.
– Indicates the absence of a systolic flow in the left atrium.
* The P value was calculated by the Fisher probability test.

tion, the sensitivity increased to 88 per cent (15/17).

Discussion

The applicability of pulsed Doppler echocardiography to the study of mitral valve lesions was first shown by Johnson *et al.*, in 1973. More recently, Kalmanson *et al.* (1975, 1977) using transseptal Doppler ultrasound catheterisation and transcutaneous pulsed Doppler method described different patterns of flow curves which they related to the severity of mitral stenosis as assessed by clinical and haemodynamic studies. The present study correlates the results of external Doppler analysis to the severity of mitral valve stenosis and regurgitation as assessed in all patients by catheterisation.

I: MITRAL STENOSIS

The maximum Doppler shift that can be detected is governed by sampling theory concepts, that is the pulse repetition rate must be twice the highest expected Doppler shift. Since the pulse repetition rate has to be lower with increasing transcutaneous depth of the sample volume, it can be postulated that some of the high-velocity jets encountered in mitral stenosis could not be recorded deep in the thorax especially when the angle is close to zero. However, the recorded velocity represents the average of velocities in the sample volume that is the mean forward flow. The plus or minus flow caused by swirling and eddying are expected to neutralise in part because of the size of the sample volume and because of the motion of the heart within the chest wall. In none of the patients studied was the flow curve observed to saturate.

In sinus rhythm, Doppler analysis detected all cases of mitral stenosis and no false positive recordings were observed. Moreover, semiquantification was achieved and statistically significant differences were found according to the degree of stenosis. The flow curves in atrial fibrillation could not differentiate patients with mild mitral stenosis from those without a mitral valve gradient. However, patterns of flow in moderate and severe stenosis resembled patterns in sinus rhythm and the haemodynamic gradients were also comparable. The method in atrial fibrillation, if not accurate for the detection of mild mitral stenosis, appears useful for the semiquantification of the degree of stenosis. Though the mitral valve gradients of a few patients with each Doppler pattern overlap, the method appears promising as a clinical adjunct for assessing the severity of mitral stenosis. Further work is needed to refine the analysis of the flow curves in order to improve their diagnostic value.

The criteria of severity for mitral stenosis previously described (Kalmanson *et al.*, 1975, 1977) included indentations on the flow curve, a decreased rate of rise of flow velocity, and a large A wave. It was reported that the greater the severity of the stenosis the more obvious were these abnormalities. Our flow patterns were grossly similar but had notably different characteristics which were useful in assessing the degree of mitral stenosis. If an increased amplitude of the atrial flow wave was observed in mild mitral stenosis, this atrial wave disappeared with more severe degrees of stenosis. It was sometimes observed in moderate or severe stenosis but then seemed clearly related to the audio signal from the mitral valve leaflets. Slight adjustment of the sample volume restored a pure signal and the so-called atrial wave disappeared. Severe stenosis was associated with a quick ascending limb followed by a slowly ascending plateau. These differences from previously reported curves could be explained in several ways. First the site of the sample volume appears critical for the quality and the reproducibility of the curve and this was not emphasised in previous work. Ultrasounds reflected from moving structures in the left ventricle may introduce artefacts in the filling curves. Secondly, the derived analogue curve represents the mean of the velocities in the sample volume and the method of zero crossing analysis may differ between different apparatus. Thirdly, the difference in the characteristics of the filter used to suppress noise may alter the pattern of the flow curve.

II: MITRAL REGURGITATION

So far, pulsed Doppler evaluation of mitral regurgitation has been explored by 2 methods. The first, described by Johnson *et al.* (1973), consists of identifying a regurgitant flow in the left atrium with the transducer located in the parasternal position. More recently Stevenson *et al.* (1977) used this approach to differentiate mitral regurgitation from ventricular septal defect. However, these reports have included few correlations with the objective results of angiography. In our hands, this method was satisfactory in grades 2 and 3 mitral regurgitation; only 2 cases were not recorded and they both occurred at the beginning of the study when our experience was limited. Thus they might represent poor technique rather than true false negative results. In the future a sensitivity of 100 per cent is expected for the diagnosis of moderate to severe mitral regurgitation. The 2 false-positive recordings of a systolic flow deserve further comment. We feel that they might represent flow from the pulmonary veins. Indeed, we suspect that the double echo occasionally seen on the left atrium A and M-mode echocardiogram may represent a pulmonary vein. Sampling in this area would yield a systolodiastolic flow. Careful siting of the electronic sampling gate could thus not only avoid recording this systolic flow but also characterise the nature of the double echo sometimes seen on the left atrial echocardiogram. More work is needed to define the value of the method in mild mitral regurgitation.

The other method of evaluating mitral regurgitation was described by Kalmanson *et al.* (1977) and consisted in identifying a systolic flow running away from the transducer positioned at the apex. In our study, the sensitivity and specificity of this method were significantly lower than with the parasternal approach. In particular, patterns of large mitral regurgitation were noted in the absence of angiographic reflux (Fig. 2). We think that the difficulties encountered with this approach are related to technical problems of lateral resolution with the apparatus we use. The sample volume overrides the inflow and outflow tracts of the left ventricle and a systolic flow corresponding to systolic ejection in the left ventricle may be confused with a true regurgitant flow through mitral valve. Hopefully, improvement in the pulsed Doppler technical characteristics will allow a more accurate evaluation of mitral regurgitation by this approach. Indeed, this method presents theoretical advantages in that the regurgitant flow is running in the axis of the ultrasound beam, optimising the Doppler shift of frequency. We expect that the development of a Doppler apparatus with improved signal-to-noise ratio will improve performance and also that the process for deriving the signal will be improved. Indeed, the recorded signal is a relatively poor reflection of the information contained in the audio signal. Spectral analysis of the Doppler signal should allow more adequate characterisation of the transmitral valve flow and more accurate quantification of mitral regurgitation and stenosis.

In future studies, location of the Doppler sample volume should be carefully described as well as the characteristics of the instrumentation used, particularly with respect to its filter and to the process of analysing the signal.

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Use of digitised left ventricular echocardiograms in assessment of mitral stenosis

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SUMMARY In order to establish a new echocardiographic index of the severity of mitral stenosis, left ventricular echocardiograms were digitised using manual tracing and a computer. The instantaneous left ventricular dimension was measured in 15 patients with mitral stenosis. The peak rate of change of left ventricular dimension (peak dD/dt) and the normalised peak rate (peak dD/dt/D) during early diastole were significantly lower in mitral stenosis than in normal subjects. Also, the time between the second heart sound and peak dD/dt was significantly shorter in patients with mitral stenosis than in normal subjects. Correlation between the mitral valve area calculated from the Gorlin formula and peak dD/dt/D was good, while valve area was poorly correlated with the EF slope of the anterior mitral leaflet echo. It is suggested that by continuous measurement of left ventricular dimension and of its first derivative, the reduced atrioventricular blood flow in mitral stenosis can be shown, and that peak dD/dt/D during early diastole is a possible index of its severity.

There is no doubt that echocardiography is useful and qualitatively reliable in diagnosing mitral stenosis when an adequate recording of both leaflets is obtained. This technique also provides important information for surgeons on the thickness and pliability of the valve leaflets and the size of the left ventricular outflow tract. Several investigators (Segal *et al.*, 1966; Edler, 1967; Effert, 1967; Gustafson, 1967) have claimed that the diastolic EF slope of the anterior mitral leaflet reflects the severity of mitral stenosis. As has previously been reported by others (Mary *et al.*, 1973; Cope *et al.*, 1975; Shiu, 1977), we also have frequently noticed discrepancies in patients with mitral stenosis between echocardiographic data and data obtained invasively by cardiac catheterisation and angiography. We have found that the EF slope is not a sensitive measure of the severity of mitral stenosis and is often misleading in individual patients.

We have used a new index, derived from the rate of change of the left ventricular dimension measured from echocardiograms using a computer-assisted method, which correlates well with the mitral valve area and may be useful in clinical practice.

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Methods

PATIENTS AND CARDIAC CATHETERISATION

Fifteen patients with isolated mitral stenosis were studied by cardiac catheterisation and echocardiography. There were 3 men and 12 women, ranging in age from 26 to 56 years, with a mean age of 38·7±8·9 years. Five patients had normal sinus rhythm, and the others were in atrial fibrillation. Ten normal subjects, 9 men and 1 woman, ranging in age from 15 to 31 years, with a mean age of 20·0±5·9 years, were also studied echocardiographically. All patients underwent left and right heart catheterisation. The mitral valve area was calculated using the modified Gorlin formula (Cohen and Gorlin, 1972). Cardiac output was estimated by the Fick method. Pulmonary artery wedge and left ventricular pressures were recorded simultaneously and the time delay in retrograde transmission of the wedge pressure pulse was assumed to be 0·05 s (Yang *et al.*, 1978). The mitral diastolic gradient was measured in early diastole, at end-diastole, and midway between these two points, and the average of these 3 measurements was taken as the mean gradient. This figure was averaged over 5 cardiac cycles.

ECHOCARDIOGRAPHIC METHODS

Strip-chart echocardiograms were recorded at 100 mm/s paper speed using an Aloka SSD-90 echograph and a 2·25 MHz transducer 10 mm in diameter with a repetition frequency of 1000/s. All subjects were studied in the supine position. In order to obtain a clear continuous recording of the interventricular septum and the left ventricular posterior wall, the transducer was placed in the third or fourth intercostal space at the left sternal border. The ultrasound beam was directed to identify the tip of the anterior mitral leaflet or the chordae just below the mitral leaflets as illustrated in Fig. 1. The electrocardiogram (lead II) and phonocardiogram were recorded simultaneously. These echocardiographic studies were performed less than one month before or after cardiac catheterisation.

ANALYSIS OF ECHOCARDIOGRAMS

In order to measure the instantaneous left ventricular dimension and to calculate its first derivative (dD/dt), the echocardiographic tracings were analysed by a computer. The echocardiogram was positioned on a digitising table and a stylus pen was moved along each of the two echoes representing the endocardium of the left ventricular side of the septum and the endocardium of the posterior wall of the left ventricle. Since this pen emitted ultrasonic waves, its position could be sensed by microphone-detectors fitted in the adjacent two sides of the table, and converted into electrical signals representing X and Y co-ordinates, with a resolution at 0·17 mm. This information, together with calibration signals corresponding to 10 cm, 1 s, and a correction for lack of rectilinearity in position of the echocardiogram on the digitising table, was stored by the HITAC 10-II computer.

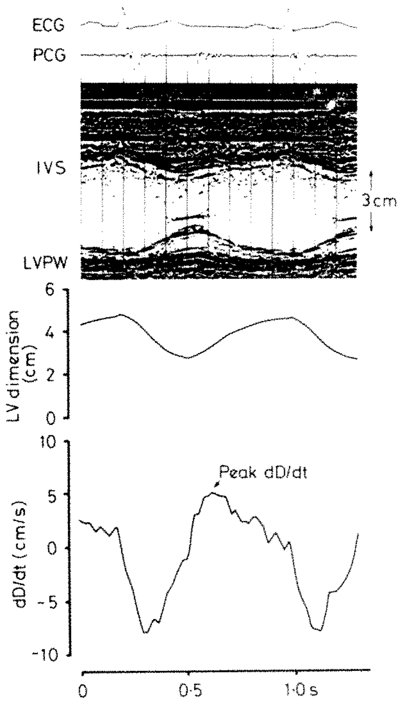

Fig. 1 *Electrocardiogram, phonocardiogram, and left ventricular echocardiogram in patient with mitral stenosis (upper). Continuous measurement of left ventricular dimension (middle) and its first derivative (dD/dt) (lower), derived as described in text. ECG, electrocardiogram; PCG, phonocardiogram; IVS, interventricular septum; LVPW, left ventricular posterior wall. Paper speed 100 mm/s.*

Linearly interpolated ordinates of one cardiac cycle was derived, corresponding to each of the two echoes, and then the ordinates of the points representing the left ventricular posterior wall echo were subtracted from those of the interventricular septum to give the instantaneous left ventricular dimension (LVD), which was displayed together with its first derivative (dD/dt) by an XY plotter (Fig. 1). Nine points least square smoothing was used to compute instantaneous values for the first derivative of the left ventricular dimension. For the present study, the following values were determined:

Table *Subjects and echocardiographic data*

	Age (y)	*Heart rate (beats/min)*	*End-diastolic dimension (cm)*	*End-systolic dimension (cm)*	*Peak dD/dt (cm/s)*	*Peak dD/dt/D* (s^{-1})	*A2-peak dD/dt time (ms)*
Normal (n = 10)	20·0 ± 5·9	63·6 ± 10·0	4·3 ± 0·3	2·8 ± 0·1	10·66 ± 1·32	3·33 ± 0·29	84·0 ± 17·4
Mitral stenosis (n = 15)	38·7 ± 8·9*	70·5 ± 11·0	4·5 ± 0·5	3·0 ± 0·4	5·89 ± 1·74*	1·76 ± 0·64*	56·0 ± 17·8*

A2, aortic component of the second heart sound; Peak dD/dt; peak rate of change of left ventricular dimension in early diastole; Peak dD/dt/D, normalised peak rate of change of left ventricular dimension.
All measurements shown as mean ± SD. * Statistical significance of difference from normal group ($P < 0·001$).

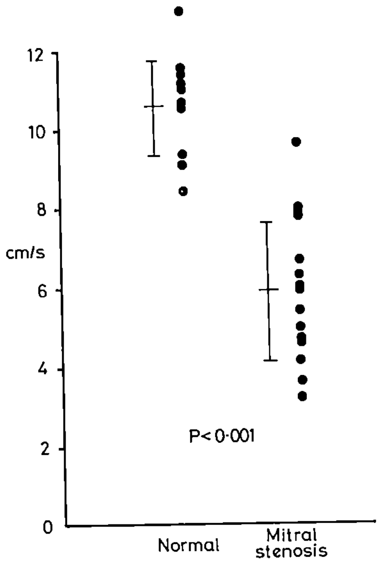

Fig. 2 *Peak dD/dt. Values shown for individual patients, with mean ± SD. This index was significantly lower in mitral stenosis than in normal subjects ($P < 0{\cdot}001$).*

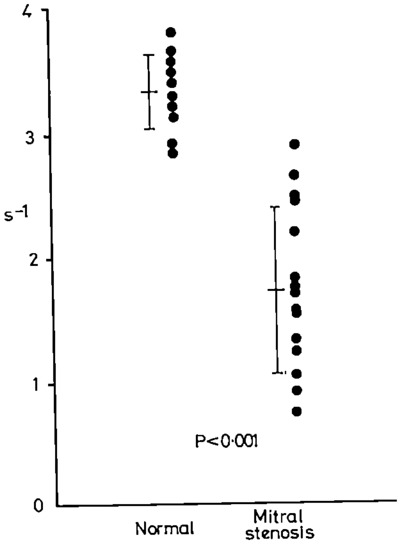

Fig. 3 *Peak dD/dt/D. Values shown for individual patients with mean ± SD. This was also significantly reduced in mitral stenosis ($P < 0{\cdot}001$). The values in patients with mitral stenosis were approximately half of those in normal subjects.*

(1) Left ventricular end-diastolic and end-systolic dimension in cm.

(2) The peak rate of change of left ventricular dimension (peak dD/dt) and the normalised peak rate (peak dD/dt/D) during early diastole in cm/s and s^{-1}, respectively. Peak dD/dt/D was obtained by dividing peak dD/dt by the instantaneous dimension at which it occurred and read directly from the print-out.

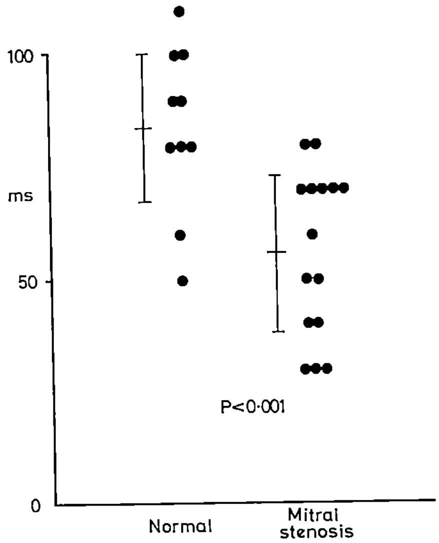

Fig. 4 *A2-peak dD/dt time. This time was significantly shorter in mitral stenosis than in normal subjects ($P < 0{\cdot}001$), and always shorter than A2-OS time.*

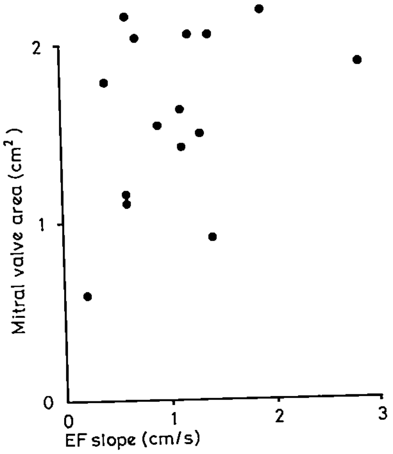

Fig. 5 *Mitral valve area vs EF slope. The EF slope correlates poorly with the calculated mitral valve area ($r = 0{\cdot}44$).*

(3) The time between the aortic component of the second heart sound and the peak dD/dt in ms (A2-peak dD/dt time).

Student's t test to determine statistical significance was performed, and the P values less than 0·05 were considered statistically significant.

Results

NORMAL SUBJECTS

In the normal group, the mean heart rate was 63·6 ± 10·0 beats/min, the left ventricular end-diastolic dimension was 4·3 ± 0·3 cm, and end-systolic dimension was 2·8 ± 0·1 cm. Peak dD/dt during early diastole was 10·66 ± 1·32 cm/s and peak dD/dt/D 3·33 ± 0·29 s^{-1}, and this occurred 84·0 ± 17·4 ms after aortic closure (A2-peak dD/dt time). These results are given in detail in the Table.

MITRAL STENOSIS

The most striking abnormality in this group was a reduction in the peak rate of change of the left ventricular dimension during early diastole (peak dD/dt) to 5·89 ± 1·74 cm/s and peak dD/dt/D to 1·76 ± 0·64 s^{-1} compared with normal subjects ($P < 0·001$) (Fig. 2, 3). A2-peak dD/dt time was 56·0 ± 17·8 ms and was also significantly shorter than in normal subjects ($P < 0·001$) (Fig. 4). Heart rate, left ventricular end-diastolic, and end-systolic dimension were 70·5 ± 11·0 beats/min, 4·5 ± 0·5 cm, and 3·0 ± 0·4 cm, respectively. These values did not differ significantly from those in normal subjects.

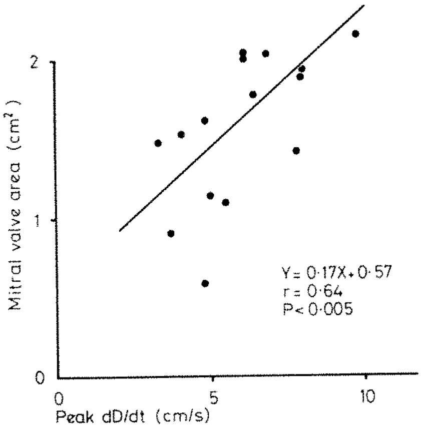

Fig. 6 *Mitral valve area vs peak dD/dt. Correlation between the calculated mitral valve area and peak dD/dt was somewhat better (r = 0·64), but there was a relatively wide scatter particularly in patients with mitral valve area less than 1·5 cm²*.

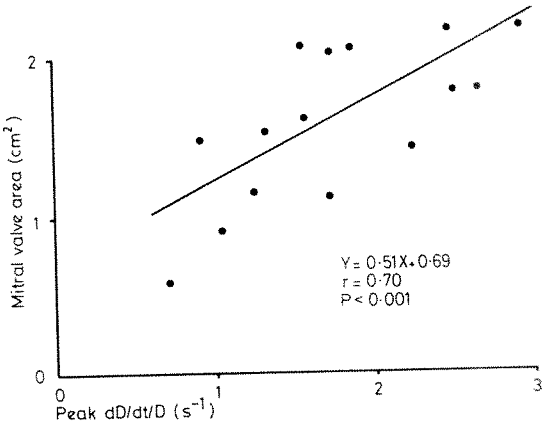

Fig. 7 *Mitral valve area vs peak dD/dt/D. There was fairly good correlation between the mitral valve area and peak dD/dt/D during early diastole (r = 0·70).*

CORRELATIONS BETWEEN ECHOCARDIOGRAPHIC AND CARDIAC CATHETERISATION DATA

The calculated mitral valve area (MVA) ranged from 0·6 to 2·2 cm^2, and the EF slope of the anterior mitral leaflet from 0·2 to 2·8 cm/s. The EF slope correlated poorly with the calculated mitral valve area ($r = 0·44$) (Fig. 5). In the same patients, the correlation between the peak rate of change of the left ventricular dimension (peak dD/dt) and the calculated mitral valve area was better ($r = 0·64$) (Fig. 6); however, there was a relatively wide scatter in patients with a mitral valve area less than 1·5 cm^2. There was much better correlation when peak dD/dt was related to the instantaneous dimension) (Fig. 7); the regression equation was:

$$MVA = 0·51 \times \text{peak dD/dt/D} + 0·69 \ (r = 0·70).$$

Discussion

Since the initial description of the echocardiographic abnormalities in patients with mitral stenosis (Edler, 1955), numerous reports have appeared. Edler observed that the diastolic EF slope of the anterior mitral leaflet in patients with mitral stenosis was conspicuously reduced compared with normal subjects. Several investigators (Segal *et al.*, 1966; Edler, 1967; Effert, 1967; Gustafson, 1967) found that this EF slope was quantitatively related to the severity of stenosis and the mobility of the valve. However, more recent investigations have shown a poor correlation between the EF slope and the severity of stenosis evaluated at cardiac catheterisation (Cope *et al.*, 1975), and it has been suggested that while the echocardiogram is a reliable method of diagnosing mitral stenosis the EF slope is an unreliable index of the severity of this lesion. Because the EF slope does not provide a satisfactory quantitative index of the severity of mitral stenosis, we studied the rate of change of the left ventricular dimension as a measure of the rate of ventricular filling, and tried to evaluate this as an index of severity. It has been shown that there is a close correlation between echocardiographic and angiographic measurements of ventricular filling in patients with a variety of forms of heart disease, and that changes in the echocardiographic left ventricular dimension may be taken as an index of ventricular filling (Gibson and Brown, 1973, 1975). This method has also been used to assess diastolic function of the left ventricle in patients with hypertrophic cardiomyopathy, in which slow ventricular filling has been shown (St. John Sutton *et al.*, 1978), and to study the genesis of the third heart sound (Furukawa *et al.*, 1977). Using this method of measurement of the rate of left ventricular filling, we found that peak dD/dt in early diastole, occurring at the time of peak atrioventricular flow, was reduced in patients with mitral stenosis to a half of that in normal subjects. We also found that peak dD/dt occurred earlier in patients with mitral stenosis than in normal subjects. This A2-peak dD/dt time was always 10 to 60 ms less than A2-OS time. These results suggest that in mitral stenosis, peak ventricular filling rate is much reduced and that this peak occurs before the opening snap. Our results confirm those of Gibson and Brown (1973) in showing that this technique is useful for evaluating ventricular filling.

The correlations between the echocardiographic indices, peak dD/dt and peak dD/dt/D, and the calculated mitral valve area were fairly good. The correlation coefficient between peak dD/dt/D and valve area was highest ($r = 0{\cdot}70$), and we suggest that this measurement may be a valid index of the severity of mitral stenosis. On the other hand, the EF slope of the anterior mitral leaflet echo correlated poorly with the calculated mitral valve area ($r = 0{\cdot}44$). In mitral stenosis, the valve leaflets are thickened and rigid, fused at their commissures, attached to thickened chordae, and often calcified. After opening, the valve leaflets probably move little relative to the valve ring, and the EF slope of the anterior mitral leaflet is thought to be profoundly influenced by mitral ring movement (Zaky *et al.*, 1968; Chakorn *et al.*, 1972). This view is supported by the analogous motion of the cage of a mitral prosthetic valve which is a rigid structure sutured to the valve ring. The rate of diastolic descent of the cage and ball is much reduced in the absence of significant obstruction across the prosthesis. If the movement of the anterior mitral leaflet in mitral stenosis is indeed related to movement of the valve ring, it is not surprising that the EF slope has little relation to the mitral valve area (Mary *et al.*, 1973; Cope *et al.*, 1975; Shiu, 1977).

Because of the unreliability of the EF slope as a measure of the severity of mitral stenosis, Shiu (1977) proposed another index. He derived a mitral valve closure index calculated from the rate of approximation of the anterior and posterior mitral leaflets, and found that this was closely related to the severity of mitral stenosis. Though the posterior mitral leaflet moves anteriorly during diastole in most patients with mitral stenosis, it moves posteriorly in some patients, as in normal subjects. Furthermore, identification of the posterior mitral leaflet is difficult in some cases of mitral stenosis. In these cases, Shiu's index may be inaccurate. Strunk *et al.* (1977) tried to assess the severity of mitral stenosis and prosthetic mitral valve obstruction from the posterior aortic wall echo. They derived an atrial emptying index from this echo and found that it correlated well with the calculated mitral valve area; this index was also useful in detecting dysfunction of the prosthetic mitral valve.

In this study we used the Gorlin formula. However, this may be a possible source of inaccuracy, particularly as the pulmonary artery wedge pressure was measured as a substitute for direct measurement of left atrial pressure. Resulting errors in calculation of mitral valve area may reduce the correlation between echocardiographic and haemodynamic indices of severity. Diastolic filling rate may be difficult to measure in those patients with severe mitral stenosis and abnormal septal movement (Weyman *et al.*, 1977), and may not measure severity of mitral stenosis in those with impaired left ventricular function who show an abnormal left contraction and relaxation pattern in the posterobasal area of the left ventricle (Heller and Carleton, 1970), and in the presence of other valve lesions. However, in other patients measurement of peak dD/dt/D was useful for evaluating the severity of mitral stenosis. The computer-assisted technique used in this study to obtain instantaneous measurement of the left ventricular dimension with its rate of change was quick and simple to carry out.

We agree with previous authors (Mary *et al.*, 1973; Cope *et al.*, 1975; Shiu, 1977) that the EF slope of the anterior mitral leaflet echo is an unreliable index of the severity of mitral stenosis. On the other hand, in the present study the rate of change of left ventricular dimension reflected the functional haemodynamic disturbance in mitral stenosis. Furthermore, the normalised peak rate of change of this dimension (peak dD/dt/D) in early diastole correlated well with the calculated mitral valve area, and may, therefore, be a reliable predictor of the severity of mitral stenosis.

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Heart rhythm during permanent cardiac pacing

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SUMMARY Heart rhythm was analysed with regard to spontaneous or pacemaker-induced heart activity, in a consecutive series of 282 patients paced for at least 1 year. The mean duration of pacing was 59 (13 to 180) months. The mean age of the patients was 76 (39 to 93) years. Spontaneous heart activity at all routine examinations was found in 33 (12%) of the patients. Pacemaker-induced rhythm only was recorded in 42 per cent of the patients whereas the remaining 46 per cent had varying electrocardiographic patterns. Of the patients with spontaneous rhythm at each visit, 10 had had complete heart block before pacing. Regular sinus activity was recorded at every routine examination in 74 per cent of the patients paced for reasons other than the sick sinus syndrome. This indicated that a substantial number of paced patients might be candidates for atrial triggered pacing. Patients treated with digitalis more often had asystole at the time of replacement of the pacemaker (32%) than those not so treated (19%). This suggests an increased risk of sudden death in paced patients on digitalis if the pacemaker fails.

Patients who require permanent cardiac pacing are generally considered to need this treatment for the rest of their lives. Several reports have, however, appeared showing that symptomatic high degree atrioventricular block sometimes is transient (Johansson *et al.*, 1963; Sowton, 1965; Donato *et al.*, 1969; Jensen *et al.*, 1973). Furthermore, long-term follow-up shows a substantial proportion of paced patients with spontaneous heart activity faster than the basic rate of the pulse generator. These observations led us to analyse the heart rhythm of a consecutive series of patients who required cardiac pacemakers because of various symptomatic bradyarrhythmias.

Subjects and methods

We included patients who had had cardiac pacemakers for at least 1 year and who were regularly followed-up at the Medical Department of Serafimerlasarettet, Stockholm. We excluded those who were paced because of tachyarrhythmias, those with atrial triggered pulse generators, and those who, during the collection of data, had moved from the region. There were 282 patients, 121 were women and 161 were men. The mean age was 76 years (range 39 to 93). Three patients were less than 50 years, 72 patients were between 51 and 70 years, and 207 patients were over 70 years. Pacemaker function was tested with electrocardiographic recordings 3 to 5 times a year. Seventy-one per cent (199) of the patients had pacemakers with a basic rate of 70/min and the remainder 60/min or less.

All electrocardiograms during permanent pacing were analysed retrospectively. Electrocardiographic recordings were made for at least 1 minute at each routine visit. Information on the indication for pacing, the stimulation rate, treatment with digitalis glycosides, and recording of intrinsic heart actvity during generator replacement was collected from the patients' records.

The electrocardiographic patterns were classed into the following 3 groups: (1) spontaneous heart activity, (2) pacemaker induced, and (3) varying heart activity, that is both spontaneous and pacemaker induced activity at either the same or subsequent follow-up visits. The appearance of ventricular ectopic beats did not influence the classification. The type of atrial activity was also noted.

A note was made of cardiac activity as seen on an oscilloscope during generator replacement with special reference to the presence of asystole during the brief period when no artificial stimulation is available. This period was not measured but it probably lasted less than 5 seconds and only on exceptional occasions was it necessary to perform external cardiac massage to maintain the circulation.

Results

The mean duration of the pacing period was 5 years (59, range 13 to 180 months). One hundred and nine patients had been paced for between 1 and 3

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years and 173 patients for more than 3 years.

Electrocardiographic findings and history of syncope before pacing are presented in Table 1; 136 patients (48%) required pacing because of complete heart block and syncope. Complete heart block was recorded in 71 per cent of the patients before pacemaker treatment was instituted. Second-degree atrioventricular block type 2 was recorded in 17 (6%), bundle-branch block in 12 (4%), and syncope of unknown cause in 6 (2%). In the bundle-branch block group, 11 patients had had syncope and 1 had disabling dizziness before pacing. Five of those patients paced because of bundle-branch block had first-degree atrioventricular block combined with bifascicular bundle-branch block. In 5 of the patients in the syncopal group, an episode of asystole had been noted without any atrioventricular block being recorded. The sixth patient in this group had had first-degree atrioventricular and had had an episode of complete heart block 16 years before the present syncopal attack.

Table 1 *Recorded electrocardiographic patterns before pacing and number of patients with syncope as indication for pacing*

	Number	*Per cent*
Complete heart block with syncope	136	71
Complete heart block without syncope	62	
Second degree atrioventricular block (type 2) with syncope	7	6
Second degree atrioventricular block (type 2) without syncope	10	
Bundle-branch block with syncope	11	4
Bundle-branch block without syncope	1	
Sick sinus syndrome with syncope	35	17
Sick sinus syndrome without syncope	14	
Syncope without known cause	6	2
Total	282	100%

Table 2 *Electrocardiographic findings during pacing in 282 patients*

	Rhythm during pacing		
Arrhythmia before pacing	*Spontaneous heart activity*	*Pacemaker induced rhythm*	*Varying*
Complete heart block	10	106	82
Second-degree atrioventricular block (type 2)	5	8	4
Bundle-branch block	4	2	6
Sick sinus syndrome	9	2	38
Syncope without known cause	5	—	1
Total	33 (12%)	118 (42%)	131 (46%)

Table 3 *Asystole at generator exchange in relation to heart activity at routine controls in 232 patients*

	Asystole	
	Number	*Per cent*
Spontaneous heart activity (n = 25)	0	0
Pacemaker induced heart activity		
> 3 years (n = 67)	36	54
< 3 years (n = 31)	6	19
Varying (n = 109)	19	17
Total (n = 232)	61	27

Table 2 shows the recorded rhythm during pacing in relation to the indication for pacemaker treatment. Thirty-three patients (12%) paced because of bradyarrhythmias had spontaneous heart activity of a higher rate than that of the pulse generator at every follow-up recording. Fourteen of these had been paced for longer than 3 years. Of the 33 patients with spontaneous heart activity all through the pacing period, 10 were paced because of complete heart block. Eight of these had had Adams-Stokes attacks.

Table 3 shows the electrocardiographic pattern of the 232 patients in whom spontaneous heart activity had been recorded during generator replacement. There were no instances of asystole in patients who had had spontaneous heart activity at routine follow-up, while 42 of the 98 patients (43%) with only pacemaker induced heart activity at follow-up suffered ventricular standstill. Patients treated with digitalis glycosides had asystole significantly more often as compared with the remainder: 32 per cent and 19 per cent, respectively ($P < 0{\cdot}05$). These 2 groups did not differ significantly with respect to age or heart size. Among patients with complete heart block and pacemaker induced rhythm at each check-up for more than 3 years, those on digitalis had a higher incidence of asystole than those not on digitalis; 68 per cent and 38 per cent, respectively ($P < 0{\cdot}05$).

Of the 233 patients paced for reasons other than the sick sinus syndrome 173 (74%) had regular sinus activity at every routine follow-up visit. Of the 75 patients who were 70 years of age or younger 47 (61%) showed continuous sinus activity. This group represented 20 per cent of all cases who were paced for an indication other than the sick sinus syndrome.

Discussion

Among patients with permanently implanted cardiac pacemakers because of symptomatic bradyarrhythmias, there are significant numbers who at routine follow-up examinations show spontaneous heart activity of a higher rate than that of their pulse generator. This finding is corroborated in our retrospective study in more than 10 per cent of our patients. Our conclusions are, however, based on recordings of heart rate and rhythm during the relatively brief routine examinations. In addition uncontrolled factors such as anxiety, inducing an increased sympathetic discharge and a subsequent increase in heart rate, may be relevant in this context in at least some patients. On the other hand, some patients with a basic pulse generator rate of 70/min might have had spontaneous heart activity if paced with a pulse generator with a lower basic rate.

A steady increase has occurred in permanent pacing of patients for reasons other than complete heart block and Adams-Stokes attacks since the first implantable pulse generator came into use 20 years ago (Elmqvist and Senning, 1960; Hori and Furman, 1977). In our series only 48 per cent of the patients were paced because of complete heart block and syncope as compared with 77 per cent in a series from Stockholm published 10 years ago (Edhag, 1969). This trend seems to exist in most countries where cardiac pacing is used extensively. One reason is the detection of more patients with the sick sinus syndrome which has been facilitated by the introduction of 24-hour electrocardiographic recording and of telemetry. In addition, increasing numbers of patients with bifascicular blocks with syncopal episodes are now being paced. Even if these groups are excluded there remains a high proportion of patients in our series with spontaneous heart activity at every follow-up visit. Therefore, even complete heart block of unknown cause may be paroxysmal or temporary. On the other hand, previous experience of the results of withdrawing pacemaker treatment in patients with advanced heart block with restored atrioventricular conduction who were experiencing pacemaker complications has been disappointing (Edhag, 1969).

When complete heart block occurs without obvious or treatable cause, for example, myocarditis or inferior myocardial infarction, permanent pacing for life is usually the only alternative contemplated. No case can yet be made for discontinuing permanent pacing after recording spontaneously conducted heart rhythm at follow-up visits, as the rhythms between checks are unknown. Grendahl and coworkers (1978) studied the escape rhythm in 92 patients treated with R wave inhibited pacemakers because of symptomatic atrioventricular block. They found a high proportion of patients with spontaneously conducted heart activity but also a discrepancy between earlier rhythm and symptoms at pacing failure. Thus, some patients had no serious symptoms in spite of a high grade of atrioventricular block and no early escape rhythm, and others had Adams-Stokes attacks at pacing failure in spite of a constant early escape rhythm at tests. Thus, as expected, knowledge of escape rhythm at an acute investigation is not conclusive in detecting patients with *permanently* spontaneous heart rhythm conduction during pacing. Furthermore, sympathetic and vagal effects probably also influence escape rhythm activity.

Regular sinus activity at every routine follow-up in 60 per cent of patients less than 70 years of age and paced for reasons other than the sick sinus syndrome point to the feasibility of atrial triggered pacing in a large number of paced patients. This is of relevance as some pacemaker patients improve significantly when treated by a system that synchronises atrial and ventricular activity (Karlöf, 1975; Moss, 1975).

As repeated findings of recorded spontaneous heart activity at each visit even during long periods still cannot exclude transient conduction failure, a diagnostic pacemaker detecting episodes of extreme bradycardia or ventricular standstill has been developed (Edhag and Vallin, 1978). This combined diagnostic and therapeutic tool makes it possible to know whether the spontaneously conducting heart rhythm is stable over long periods of time. This pacer can be programmed to a conventional lithium-powered ventricular inhibited pulse generator.

Our findings indicate that patients treated with digitalis glycosides have an increased risk of asystole during generator replacement procedures. Digitalis has been shown to have a positive inotropic effect in paced patients with cardiac failure (Benchimol *et al.*, 1965; Donoso *et al.*, 1965; Kaiser *et al.*, 1965). However, a decrease in ventricular automaticity with therapeutic doses of digitalis has been found in clinical investigations (Edelist *et al.*, 1963; Edhag and Rosén, 1969). As digitalis treatment might induce atrioventricular asynchrony resulting in worsened cardiac performance, it may be argued that diuretics alone are preferable in some paced patients.

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Effect of variation in coronary artery anatomy on distribution of stenotic lesions

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SUMMARY A relation between the proximal or distal localisation of atherosclerotic lesions and 3 anatomical variables (i) the length of the left main coronary artery, (ii) its angle of bifurcation into anterior descending and circumflex arteries, and (iii) the dominant coronary artery, was sought at coronary angiography. Studies were made on 149 angiograms of which 95 had critical stenoses ($\geq 50\%$ of vessel lumen) and the remaining 54 were either normal or contained only minimal disease.

The mean left main coronary artery length was shorter in the patients with coronary artery disease (10·6 mm) than in the normals (12·9 mm). Patients with proximal coronary artery disease (9·1 mm) had a much shorter mean left main coronary artery length than those with distal lesions alone (12·9 mm). This finding implies that a short left main coronary artery favours the proximal localisation of atherosclerotic stenoses by increasing the severity of atherogenesis proximally.

No significant difference was found between the mean angle of bifurcation of the normals (75°) and that of the total coronary artery disease group (81°). The patients with proximal disease showed a tendency towards a wider bifurcation angle (85°) than the distal disease group (76°) but this did not reach significance at the 5 per cent level.

When present in combination with a short left main coronary artery, a wide bifurcation angle was associated with a trend towards proximal localisation of stenoses over and above that of a short left main coronary artery alone.

Dominant circumflex systems had significantly shorter mean left main coronary artery lengths (9·1 mm) than had dominant right coronary arteries (12·0 mm). No effect of circumflex dominance on localisation of disease was found.

These results show that a short left main coronary artery alone constitutes an anatomical factor which favours proximal localisation of stenoses. This effect is further enhanced by its combination with a wide angle of bifurcation.

The distribution of atherosclerotic lesions has been shown both in animals (Flaherty *et al.*, 1972) and in man (Mishkin, 1967; Montenegro and Eggen, 1968) to be patchy but non-random, with stenoses being situated preferentially at branch ostia, at bifurcations, and in the proximal segments of the resulting daughter vessels. This study investigates the relation of 3 aspects of coronary artery anatomy (length of left main coronary artery; its angle of bifurcation into the left anterior descending and circumflex branches; and the dominance or otherwise of the circumflex artery) to the incidence of proximal stenoses. In view of the poor prognosis of proximal lesions and their suitability for bypass grafting (Johnson and Kayser, 1973; Takaro *et al.*, 1976), the discovery of innate anatomical risk factors which favour their formation is of importance.

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Patients and methods

Assessments were made of 161 consecutive coronary angiograms carried out at St. Thomas' Hospital by the Judkins technique. Of these, 7 were excluded as technically unacceptable and the remaining 154 comprised the study group. In a further 5 angiograms only one view of the left main coronary artery was taken and these were not included in that part of the study relating to length of left main coronary artery which was therefore based on 149 angiograms. Of these, 54 were normal or had

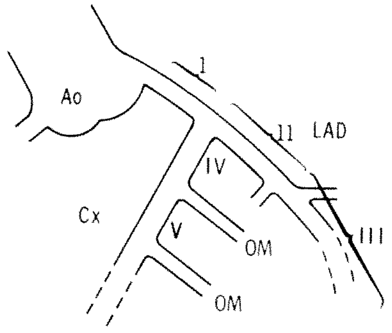

Fig. 1 *Segmentation of left coronary artery. Schematic diagram of left main coronary artery and its bifurcation into left anterior descending and circumflex arteries, displaying the extent and distribution of segments. Ao, aorta; LAD, left anterior descending artery; Cx, left circumflex artery; OM, obtuse marginal artery; Seg I, L mainstem; II, LAD proximal to first septal; III, distal LAD; IV, Cx proximal to first OM; V, distal Cx.*

minimal disease only and constituted a control group.

The left mainstem length was measured in each case from its orifice (visualised by spillback of contrast medium into the aorta during selective injection) to its bifurcation into the left anterior descending and circumflex arteries. Measurements were made in the most appropriate single frame in both the right anterior oblique and left anterior oblique projections in all patients. Correction for magnification was made by calculating the ratio of the projected diameter of the Judkins catheter to its actual diameter (from the manufacturer's data). The measured left main coronary artery lengths were then divided by this ratio and the longest corrected measurement in either the right anterior oblique or left anterior oblique views was taken as the true left main coronary artery length. In 63 patients a left cranio-caudal view was also available and the left main coronary artery length obtained in these was compared with the longer value from either the right anterior oblique or left anterior oblique view.

Each left coronary artery was divided into 5 segments (see Fig. 1). The severity of all atheromatous lesions was assessed and their distribution in these segments noted. A lesion was deemed critical if it reduced the measured luminal diameter by 50 per cent or more in 2 views when compared with the diameter of the contiguous normal vessel lumen. Such lesions located in segments I, II, and IV were considered proximal and those in segments III and V distal.

The projected radiological angle between the origins of the left anterior descending and circumflex arteries (bifurcation angle) was measured with a protractor in the right anterior oblique view. The dominant coronary artery (either right coronary artery or circumflex) was defined as the vessel supplying either the atrioventricular node branch or the posterior descending artery if the former was not discernible and was noted in each case.

In order to assess the influence of the combination of left main coronary artery length and bifurcation angle on the proximal localisation of disease, the angiograms were divided into those with a short left main coronary artery (less than the mean length of 10·6 mm for the coronary artery disease group) and those with a long left main coronary artery (> 10·6 mm). The groups so formed were then subdivided according to the presence of a wide bifurcation angle (greater than the mean angle of 81° for the coronary artery disease group) or a narrow one (< 81°). The distribution of stenoses in each of the 4 resulting subgroups was noted (see Table 3).

Table 1 *Mean left main coronary artery length in relation to presence and site of coronary artery disease*

	All normal patients	*All coronary artery disease patients*	*Prox. coronary artery disease patients*	*Non-prox. coronary artery disease patients*
Number of cases	54	95	56	39
Mean left main coronary artery (mm)	12·9	10·6	9·1	12·9
P value	< 0·05		< 0·005	

Table 2 *Mean bifurcation angle in relation to presence and site of coronary artery disease*

	All normal patients	*All coronary artery disease patients*	*Prox. coronary artery disease patients*	*Non-prox. coronary artery disease patients*
Numbers	54	92	53	39
Mean bifurcation angle	75°	81°	85°	76°
P value	< 0·1		0·05 < P < 0·1	

Table 3 *Site of coronary artery disease in relation to various combinations of left main coronary artery length and angle of bifurcation*

	All coronary artery disease patients (92)		*Short left main coronary artery plus wide angle (23)*		*Short left main coronary artery plus narrow angle (24)*		*Long left main coronary artery plus wide angle (32)*		*Long left main coronary artery plus narrow angle (13)*	
	No.	%	*No.*	%	*No.*	%	*No.*	%	*No.*	%
Prox. coronary artery disease	53	58	18	78	15	63	16	50	4	31
Distal coronary artery disease	39	42	5	22	9	37	16	50	9	69

Statistical analysis

The results were analysed using the test for the significance of the difference between the means of 2 large samples or a χ^2 test combining 2 × 2 tables when necessary.

Results

Of the 149 angiograms studied, 95 showed critical stenoses of which 56 (59%) were proximal and 39 (41%) were distal. The remaining 54 angiograms were either normal or had non-critical minor disease only.

(a) LENGTH OF LEFT MAIN CORONARY ARTERY

The mean lengths of the left main coronary arteries in relation to the presence and site of coronary artery disease are shown in Table 1. The mean length in the 95 patients with coronary artery disease was 10·6 mm which was significantly shorter ($P < 0·05$) than that of the normals (12·9 mm). The group with proximal lesions had much shorter ($P < 0·005$) left main coronary arteries (9·1 mm) than those with distal lesions alone (12·9 mm).

The frequency distribution of left main coronary artery lengths is displayed in Fig. 2 which contrasts the patients with proximal disease with those having distal lesions. This distribution is bimodal. The patients with coronary artery disease predominantly have shorter left main coronary arteries (8 to 10 mm) than the patients with distal coronary artery disease who form a separate group with longer left main coronary arteries (12 to 14 mm). An immediate bifurcation was found radiologically in 8·4 per cent of cases. This contrasts with the pathological study of Penther *et al.* (1977) in which no case of immediate bifurcation was found.

(b) ANGLE OF BIFURCATION

All of the 54 control angiograms and 92 of the 95 critically diseased angiograms had measurable bifurcation angles in the right anterior oblique projection. The mean angles found in relation to the presence and site of coronary artery disease are shown in Table 2. The difference between the mean bifurcation angle in the normals (75°) and the total coronary artery disease group (81°) was not significant ($P > 0·1$). However, the mean angle in the patients with proximal disease (85°) was wider than that in the group with distal stenoses alone (76°) though the difference did not reach significance at the 5 per cent level ($0·05 < P < 0·1$).

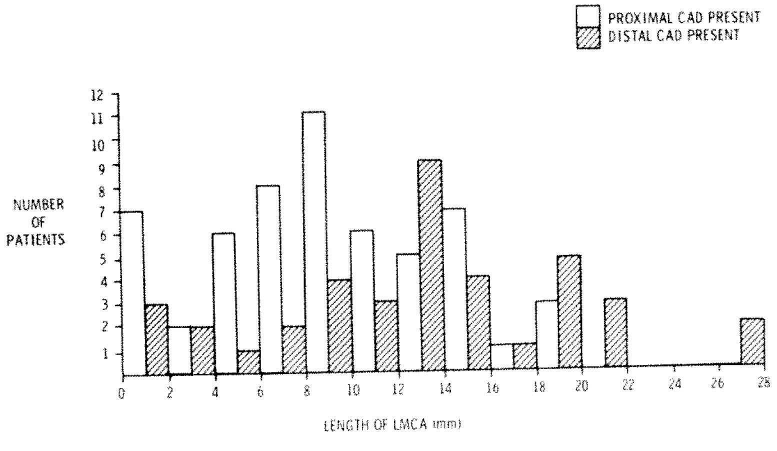

Fig. 2 *Length of left main coronary artery in 95 patients with coronary artery disease—comparison between vessels with proximal and distal disease showing bimodal distribution.*

(c) COMBINATION OF LEFT MAIN CORONARY ARTERY LENGTH AND BIFURCATION ANGLE

The site of coronary artery disease in relation to the various combinations of left main coronary artery length and bifurcation angle is shown in Table 3. This shows that the greatest proximal localisation of stenoses (78%) was found when a combination of a short left main coronary artery with a wide bifurcation angle existed, and the tendency toward proximal distribution was slightly greater for this combination than for a short left main coronary artery alone ($0\cdot05 < P < 0\cdot1$).

(d) ARTERY OF DOMINANCE

Of the 149 patients studied, 23 (15%) had a dominant circumflex artery and in this group the mean left main coronary artery was 9·1 mm. This was significantly shorter ($P < 0\cdot05$) than in the 126 patients with a dominant right coronary artery (or mixed dominance) 12·0 mm. Among the group with coronary artery disease, no difference in the prevalence of proximal lesions was found between those with a dominant circumflex (9 out of 15, 60%) and those without (47 out of 80, 59%).

(e) COMPARISON OF LEFT MAIN CORONARY ARTERY LENGTH IN DIFFERENT VIEWS

In the 64 angiograms having right anterior oblique, left anterior oblique, and left cranio-caudal views, the mean left main coronary artery length in the left cranio-caudal projection was 12·2 mm which did not differ significantly ($P > 0\cdot1$) from that based on the longer of the other two views (10·8 mm).

Discussion

Atherosclerosis is not randomly distributed in the coronary arteries. Montenegro and Eggan (1968) in a series of 27 207 coronary arterial trees showed a much greater prevalence of stenoses in the proximal arterial segments. The peak incidence was in the first and second centimetres of the left anterior descending circumflex, and the second to third centimetres of the right coronary artery. The finding in this study that 59 per cent of lesions were proximal is in agreement with this. The mechanisms that produce this tendency to proximal distribution of atherosclerosis are not known. Haemodynamic factors, however, may be important (Blumenthal, 1967; Stehbens, 1975), especially changes in arterial wall shear stress which is proportional to flow rate. Caro *et al.* (1969) and Caro (1973) implicate regions of low wall shear which they suggest retard the efflux of intramurally synthesised lipid from the arterial wall into the blood stream. Fry (1968, 1973) reaches the opposite conclusion and regards areas of high wall shear as atherogenic. This author feels that high wall shear results in (i) damage to endothelial cells thus increasing their permeability to proteins and lipoproteins, and (ii) structural changes including intimal fibrosis, smooth muscle cell proliferation, and endothelial cell erosion with an associated exaggerated reparative process. Clearly defined regions of high and low wall shear stress (often with a sharp boundary between them) are created at the apex of bifurcations and in the proximal few centimetres of the resulting daughter branches (Brech and Bellhouse, 1973; Malcolm and Roach, in press) (Fig. 3). The length of the left main coronary artery and the angle of bifurcation are anatomical variables which alter haemodynamics and hence may affect distribution of atherosclerotic stenoses.

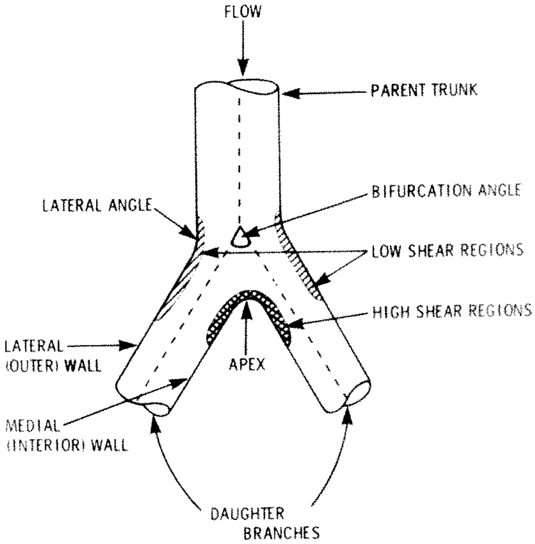

Fig. 3 *Distribution of high and low shear regions at a bifurcation and in the proximal daughter branches created by incident flow.*

Table 4 *Left main coronary artery length in previous studies*

Type of study	*Mean left main coronary artery length (mm)*	*Authors*
Angiographic	9·5	Fox *et al.* (1973)
	10·4	Kronzon *et al.* (1974)
	12·0	Furlong *et al.* (1972)
	12·8	Lewis *et al.* (1970)
	12·4	Gazetopoulos *et al.* (1976)
Pathological	10·36	Penther *et al.* (1977)
	11·4	Green *et al.* (1967)
	13·5	Baroldi and Scomazzoni (1967)
	5·5	Fox *et al.* (1973)

The mean left main coronary artery length has been estimated at angiography and necropsy in a number of reports (see Table 4). A previous angiographic study (Gazetopoulos *et al.,* 1976) based on a relatively small sample (43 patients) found a shorter mean left main coronary artery length in arteries with atheromatous lesions—but made no distinction between those with proximal and distal disease. A more recent anatomical study (Penther *et al.,* 1977) found no such relation. The present study shows that the mean left main coronary artery length is much shorter (9·1 mm) when proximal disease is present than when distal disease alone exists (12·9 mm). This implies that a short left main coronary artery favours the proximal localisation of atherosclerotic lesions. The relatively poor prognosis of such lesions and their apparent benefit from bypass grafting (Johnson and Kayser, 1973; Takaro *et al.,* 1976) make this relation important.

Two complementary mechanisms probably underlie this relation. Firstly, by Poiseuille's equation, the length of a rigid pipe through which a Newtonian fluid flows is directly proportional to the pressure drop in the pipe and inversely related to the volume flow along it. Consequently, the shorter the pipe the smaller the pressure drop and the larger the flow. However, the application of this equation to flow in human blood vessels has certain limitations since blood is a non-Newtonian fluid and the vessels are non-rigid (distensible). None the less, within the physiological range in vessels greater than 0·1 cm internal diameter, blood behaves to a large extent in a Newtonian fashion (Haynes and Burton, 1959; McDonald, 1974), and these relations hold good. Thus a short left main coronary artery results in a small pressure drop and a large flow at the bifurcation. The resulting high wall shear favours atherogenesis (Fry, 1968) at the bifurcation and in the proximal segments of the daughter branches (left anterior descending and circumflex). A long left main coronary artery has the opposite effect and causes increased pressure drop, reduced flow, and hence low wall shear at the bifurcation. This may be protective against atheroma formation.

Secondly, Tjotta (1963), Nordenström (1966), and Gazetopoulos *et al.* (1976) have pointed out that lesions localise in areas of systolic kinking and motion. The proximal segments of the left anterior descending and circumflex are relatively untethered and hence prone to excess systolic bending. In addition, their lengths are inversely proportional to the mainstem length. Thus a short left main coronary artery is associated with long untethered proximal segments in the left anterior descending and circumflex which may then be prone to excessive systolic motion and hence to increased risk of atheromatous degeneration.

The importance of the angle of bifurcation in altering haemodynamics and hence atherogenesis has been investigated experimentally (Brech and Bellhouse, 1973; Malcolm and Roach, in press). These latter workers used a family of glass models with bifurcation angles varying from 45° to 180°. They confirmed the apex and proximal medial wall of the daughter branches as sites of high flow and high shear and the lateral angles as low flow areas of low shear (Fig. 3). At these angles separation of fluid streamlines move away from the lateral walls (boundary layer separation) to leave an underlying space. This separated region contains fluid streamlines reflected from daughter branches. Flow velocity and wall shear are low in this region. Further, they showed that the magnitude of boundary layer separation with its associated low shear separated regions was increased by (a) asymmetry or irregularity of the bifurcation, (b) imbalance of the relative flows down the daughter branches (a common situation in nature), and notably by (c) increasing angle of bifurcation. In addition, turbulence and vortex formation in daughter branches were greater in the models with wider bifurcation angles.

Thus by alteration of local shear forces and turbulence in the proximal daughter branches, especially under conditions of flow imbalance, the angle of bifurcation theoretically exerts an important effect on the localisation of stenoses. In the present study, the mean bifurcation angle was wider in the group with proximal disease (85°) than in the group with distal disease (76°) ($0{\cdot}05 < P < 0{\cdot}1$) though this did not reach significance at the 5 per cent level. Similarly, in combination with a short left main coronary artery, a wide angle exerted a small additional influence favouring proximal localisation over and above that of a short left main coronary artery alone ($0{\cdot}05 < P < 0{\cdot}1$). The radiological assessment of the bifurcation angle in the right anterior oblique view did not reflect the true angle since the parent trunk (left main coronary artery) and daughter branches (left anterior descending and circumflex) ran in different planes and the directions often overlapped. These factors reduce the possibility of obtaining a significant association.

The mean left main coronary artery length (9·1 mm) was significantly shorter ($P < 0{\cdot}05$) in the group with dominant circumflex arteries than in the right coronary artery group (12·0 mm). This angiographic finding is in close agreement with that of Kronzon *et al.* (1974) but contrary to the result of the pathological study of Penther *et al.* (1977).

Despite the finding of shorter mean left main coronary artery length, dominant circumflex systems were not associated with a higher prevalence of proximal disease in this study. The explanation for this may lie in the small sample size (15 patients with coronary artery disease and a dominant circumflex artery). Alternatively, an effect of this configuration negating the influence of a short left main coronary artery and hence protecting against proximal distribution of disease could be postulated. This, however, would be contrary to the angiographic findings of Gensini and Buonanino (1968) that lesions in the circumflex artery were more frequent and severe when it was dominant.

Thus coronary artery anatomy may play an important role in the pathogenesis and localisation of demonstrated lesions. In addition, the rate of progression of proximal disease may be strongly influenced by anatomical characteristics of the coronary arteries. Angiographic definition of this anatomy may prove predictive of an enhanced rate of proximal progression of lesions by showing a configuration favouring further proximal disease.

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Patterns of atrial activation during right ventricular pacing in patients with concealed left-sided Kent pathways

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SUMMARY A 'concealed' accessory pathway was suspected in 12 patients because of eccentric left atrial activation during tachycardia. Retrograde conduction during ventricular pacing may occur over the atrioventricular node, the accessory pathway, or both. There were 4 patterns of ventriculoatrial conduction in response to ventricular extrastimuli (V_2) at various coupling intervals: (1) exclusive accessory pathway conduction throughout the cardiac cycle in 2 patients; (2) exclusive accessory pathway conduction at long coupling intervals and exclusive atrioventricular node conduction at short coupling intervals in 2 patients; (3) variably fused accessory pathway/atrioventricular node conduction at long coupling intervals but exclusive accessory pathway conduction at short coupling intervals in 4 patients; (4) fused accessory pathway/atrioventricular node conduction at long coupling intervals but exclusive atrioventricular node conduction at short coupling intervals in 4 patients.

With increased prematurity of V_2 the ventricle to right atrial interval prolonged conspicuously in 11 of 12 patients whereas the ventricle to left atrial interval remained constant until the refractory period of the accessory pathway in all but 2 instances where intraventricular delay occurred. This study emphasises the importance of left atrial recordings in these patients.

It is now well recognised that concealed ventriculoatrial anomalous pathways provide the anatomical substrate for a large proportion of paroxysmal reentrant tachycardias (Slama *et al.*, 1973; Spurrell *et al.*, 1974; Rowland *et al.*, 1977). These pathways are designated 'concealed' because they do not conduct anterogradely and therefore there are no electrocardiographic signs of ventricular preexcitation. They do, however, produce atrial preexcitation in response to ventricular stimulation. The degree of atrial pre-excitation via a concealed accessory pathway is dependent upon tissue refractoriness and conduction times from the point of ventricular stimulation to the atrial recording site. Constancy of the ventriculoatrial conduction time has been used as a criterion for conduction in an anomalous ventriculoatrial pathway, but evidence in patients with overt Wolff-Parkinson-White syndrome (Tonkin *et al.*, 1975; Sung *et al.*, 1977a) suggests that this criterion taken by itself may result in underdiagnosis of concealed ventriculoatrial pathways.

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This study was designed to investigate retrograde conduction patterns in patients with concealed ventriculoatrial pathways.

Patients and methods

The 12 patients were admitted for investigation of recurrent paroxysmal tachycardias. Clinical details are summarised in Table 1. In all patients physical examination, chest radiography, and routine haematological investigations were normal. In 5 patients the PR interval was short and in 7 patients it was normal. The QRS complex during sinus rhythm was normal in all patients.

All patients were studied in the post-absorptive, non-sedated state and medications were discontinued at least 72 hours before study. Under local anaesthetic, 4 bipolar USCI electrode catheters with 1 cm interelectrode distance were introduced via the femoral vein and positioned in the right ventricular apex, against the septal leaflet of the tricuspid valve and in the high right atrium (2 catheters). A quadripolar USCI catheter with 1 cm interelectrode distances, was inserted via the left

Table 1

Case no.	*Age, sex*	*symptoms*	*ECG PR (s)*	*QRS*	*Documented arrhythmias*
1	48, M	Palpitation	0·20	N	SVT
2	40, F	Palpitation and dizziness	0·11	N	SVT, AF
3	21, F	Palpitation	0·12	N	SVT
4	50, M	Palpitation	0·18	N	SVT, AF
5	41, M	Palpitation	0·12	N	SVT
6	47, F	Palpitation	0·20	N	SVT
7	39, M	Palpitation	0·19	N	SVT
8	54, F	Palpitation	0·21	N	SVT
9	40, F	Palpitation	0·20	N	SVT
10	47, M	Palpitation	0·12	N	SVT
11	63, M	Palpitation	0·11	N	SVT, AF
12	15, F	Palpitation	0·16	N	SVT

N, normal; SVT, supraventricular tachycardia; AF, atrial fibrillation.

basilic vein and positioned in the coronary sinus. Electrograms from the intracardiac catheters were recorded on a 16-channel Elema Mingograf recorder at a paper speed of 100 mm/s together with surface electrocardiographic leads I, aVF, V1, and V6. Intracardiac signals were filtered between 50 and 700 Hz. Stimulation was performed using a Devices 4270 isolated stimulator with pulse widths of 1·5 to 2 ms at a voltage approximately twice the diastolic threshold.

In all patients anterograde and retrograde conduction studies were performed using the extra-stimulus technique (Durrer *et al.*, 1967). Retrograde conduction was studied during right ventricular apical pacing. The ventriculoatrial conduction times were measured from the onset of ventricular activation to the earliest clearly distinguishable atrial electrogram in the right atrium (V-RA) and coronary sinus (V-LA). The earliest point of atrial activation during sustained tachycardia was taken as indicating the approximate location of the accessory pathway. This point was determined by coronary sinus withdrawal mapping. The atrial activation sequence during tachycardia was considered to represent atrial depolarisation by exclusive conduction in the accessory pathway (Fig. 1).

Rapid atrial pacing at right and left atrial sites was performed in all patients. In 7 patients atrial fibrillation was induced electively. Anterograde

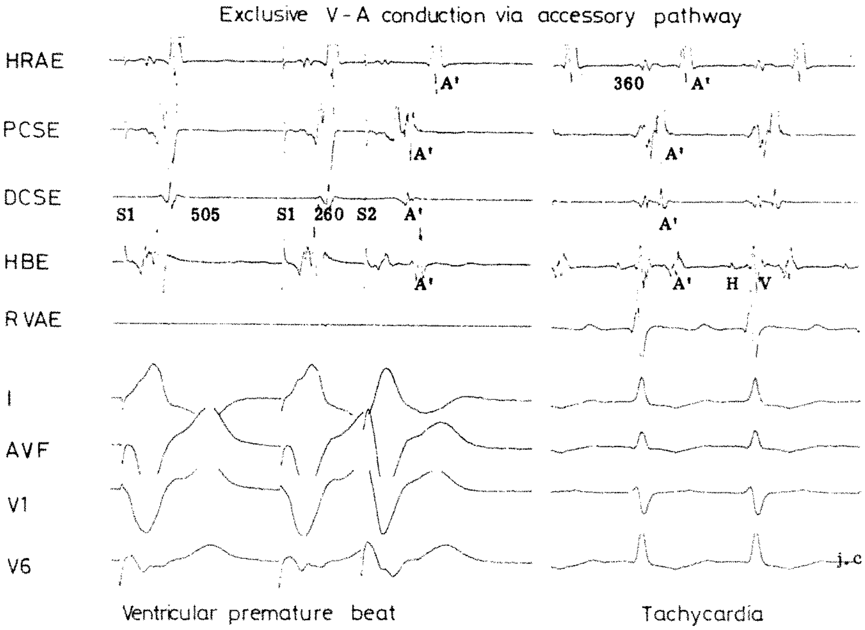
Exclusive V-A conduction via accessory pathway
HRAE
PCSE
DCSE
HBE
R VAE
I
AVF
V1
V6
A'
360
S1
505
S1
260
S2
H
V
j.c
Ventricular premature beat
Tachycardia

Fig. 1 *Comparison of atrial activation sequence after a ventricular premature beat* (left panel) *and during tachycardia* (right panel) *in case 3 (group 3). A ventricular premature stimulus (S_2) at 260 ms coupling interval after a regular paced sequence (S_1-S_1) results in retrograde atrial activation (A') identical to that seen during re-entrant tachycardia. HRAE, high right atrial electrogram; PSCE, proximal coronary sinus electrogram; DCSE, distal coronary sinus electrogram; HBE, His bundle electrogram; RVAE, right ventricular apex electrogram (not recorded during ventricular pacing). I, AVF, V1, V6 = surface electrocardiographic leads.*

conduction in the accessory pathway was excluded by the lack of pre-excitation in response to atrial stimulation near the accessory pathway (Boineau *et al.*, 1973; Denes *et al.*, 1977) and in 7 patients by the absence of pre-excitation during atrial fibrillation. Retrograde conduction curves were obtained by plotting the values of V-LA and V-RA and the corresponding intervals between successive atrial electrograms in response to the premature stimulus V_2 against the coupling interval V_1-V_2 of the extrastimulus.

Results

The results are summarised in Table 2.

In all 12 patients re-entrant atrioventricular tachycardia was initiated by a single atrial premature stimulus. In 5 patients a right ventricular apical stimulus was also effective in initiating tachycardia. Earliest atrial activation during tachycardia was in the coronary sinus recording in all 12 patients: proximal coronary sinus in 7 patients and distal coronary sinus in 5 patients. The low right atrial electrogram could be clearly seen during tachycardia in all 12 patients and followed the earliest atrial electrogram in the coronary sinus region.

Retrograde atrial activation patterns during right ventricular pacing and programmed extrastimulation were of 4 different types (Table 2).

GROUP 1

In this group of 2 patients, the ventriculoatrial intervals remained constant at all coupling intervals (V_1-V_2) of ventricular extrastimuli (V_2). In 1 patient there was a small but equal increase in the V-LA and V-RA conduction times at very short coupling intervals. The relation between the right and left atrial electrograms did not change. In both patients tachycardia was initiated by a programmed atrial or ventricular premature beat. The atrial activation sequence during tachycardia was identical to that observed during programmed ventricular extrastimulation. The retrograde conduction curve from one of these patients is shown in Fig. 2a.

Table 2

Case no.	*Site of AP*	*Mode of initiation of tachycardia*	*Pattern of atrial activation (VPBs)*	*Group*
1	Distal CS	APB	F →AVN	4
2	Distal CS	APB, VPB	F →AP	3
3	Proximal CS	APB	F →AP	3
4	Proximal CS	APB	AP→AVN	2
5	Distal CS	APB	F →AVN	4
6	Proximal CS	APB	AP→AVN	2
7	Proximal CS	APB, VPB	AP→	1
8	Proximal CS	APB, VPB	F →AP	3
9	Distal CS	APB	F →AVN	4
10	Proximal CS	APB	F →AVN	4
11	Proximal CS	APB, VPB	AP→	1
12	Distal CS	APB	F →AP	3

AP, accessory pathway; CS, coronary sinus; AVN, AV nodal; F, fusion; APB, programmed atrial premature beat; VPB, programmed ventricular premature beat.

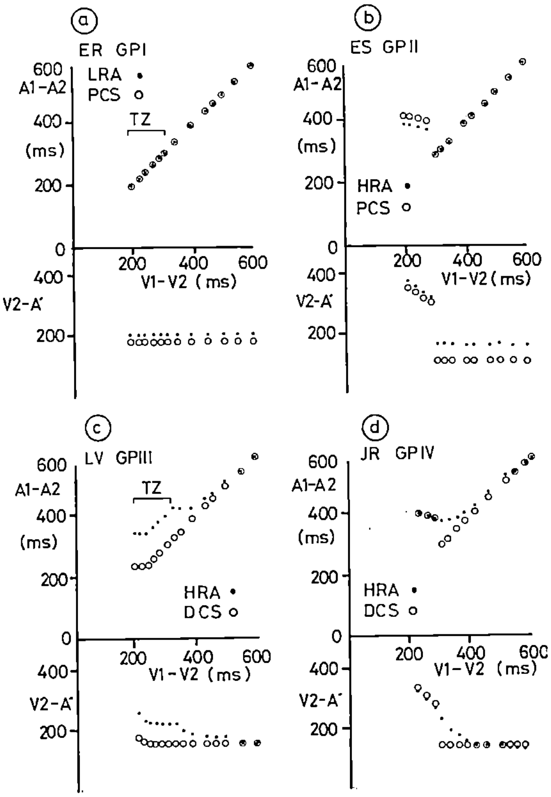

Fig. 2 *Retrograde conduction curves from patients representing each of the 4 groups. For discussion see text. LRA, low right atrial electrogram; HRA, high right atrial electrogram; PCS, proximal coronary sinus electrogram; DCS, distal coronary sinus electrogram; TZ, tachycardia zone.*

GROUP 2

In 2 patients, the V-LA and V-RA conduction intervals remained more or less constant at long coupling intervals of V_2. At shorter coupling intervals there was a sudden increase in the V-LA and V-RA intervals. At all values of V_1-V_2 shorter than that which resulted in the sudden increase in the ventriculoatrial intervals, there was a progressive smooth increase in the ventriculoatrial conduction times without a further change in the relation of the atrial electrograms (Fig. 2b). In this group, tachycardia could not be initiated by a ventricular premature stimulus but was reliably initiated by a single atrial premature stimulus. In 1 of these patients the atrial activation sequence during tachycardia was identical to that observed with premature beats in the range of coupling intervals which resulted in constant ventriculoatrial intervals. In the other patient (case 4), the recordings were difficult to interpret partly because the low right atrial electrogram was not clearly seen. These recordings are shown in Fig. 3 and the results presented graphically in Fig. 4.

GROUP 3

In 4 patients various degrees of atrial fusion (V-LA and V-RA not changing concordantly) were seen in response to longer coupling intervals of V_2. As the coupling interval of V_2 was reduced, the V-RA interval increased gradually but the V-LA interval remained constant. Further decreases in the V_1-V_2 interval resulted in an attenuation of the increase in V-RA time which gradually plateaued, forming a curve parallel to the V-LA curve (Fig. 2c). The V-LA interval remained constant throughout in 2 patients, with a small increase in V-LA and V-RA intervals at very short coupling intervals in 1 patient. In case 3 this basic pattern was modified (Fig. 5). At coupling intervals greater than 360 ms (Fig. 5 and 6) low right atrial activation was progressively delayed as V_1-V_2 was decreased. At 360 ms, there was a sudden increase in the V-RA interval which remained constant with coupling intervals, V_1-V_2 between 360 and 320 ms. The V-LA interval remained unchanged. At V_1-V_2 of 300 ms the V-RA interval shortened again and increased as V_2 become more premature. Coupling

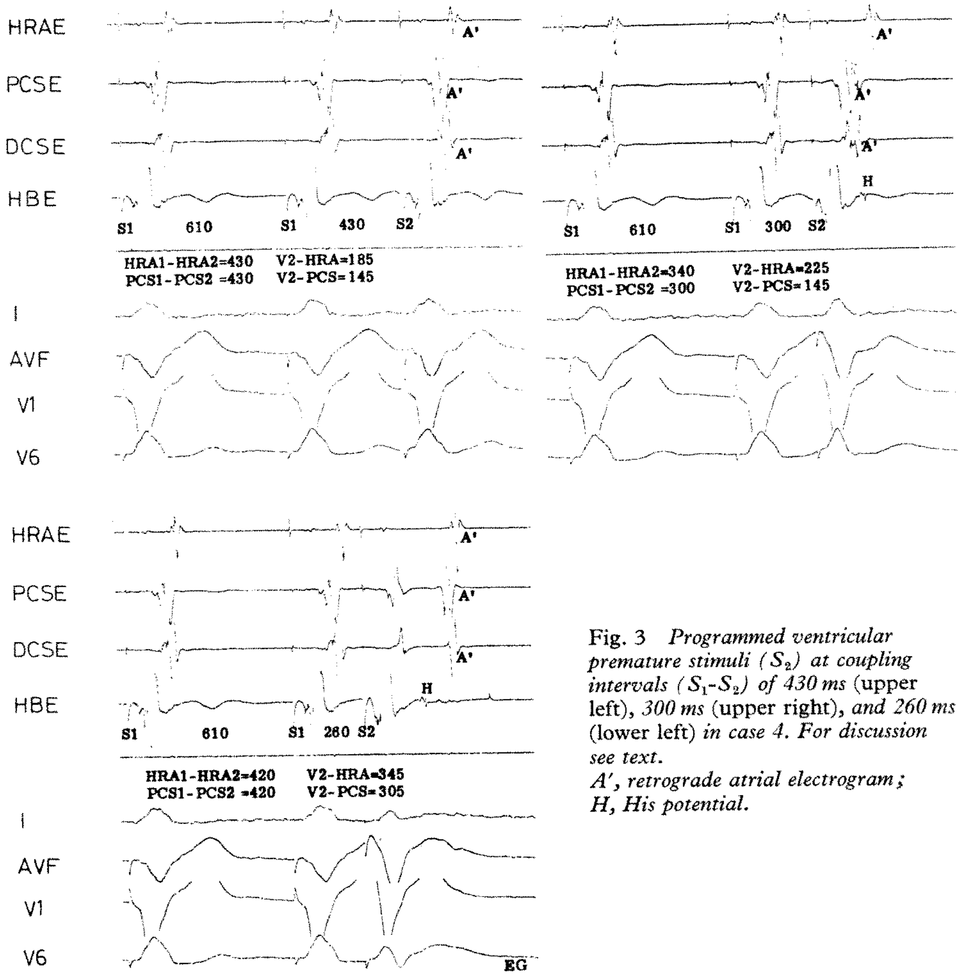

Fig. 3 *Programmed ventricular premature stimuli* (*S_2*) *at coupling intervals* (*S_1-S_2*) *of 430 ms* (upper left), *300 ms* (upper right), *and 260 ms* (lower left) *in case 4. For discussion see text.*
A', retrograde atrial electrogram; H, His potential.

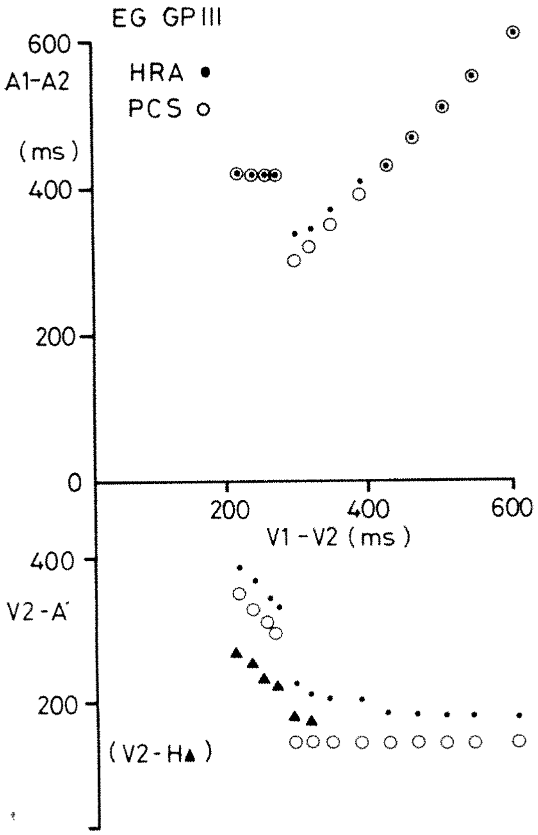

Fig. 4 *Retrograde conduction curve of case 4 (group 2). For clarity H_1-H_2 intervals are omitted; the V-H interval is plotted on the lower part of the graph. For discussion see text.*

intervals of V_2 shorter than 260 ms did not result in any further increase in the V-RA interval (Fig. 5).

In all 4 patients in this group, re-entrant tachycardia could be initiated by a single atrial premature beat but a single ventricular extrastimulus was effective in only 3 patients. The atrial activation sequence during tachycardia was identical to that observed at coupling intervals of V_2 which resulted in parallel V-RA and V-LA curves.

GROUP 4

In the 4 patients in this group, atrial fusion was also observed at longer coupling intervals of V_2. As V_1-V_2 was decreased the V-RA interval gradually increased while the V-LA interval remained constant. At a shorter coupling interval, there was a sudden increase in the V-LA interval. Values of V_1-V_2 shorter than that which resulted in the sudden increase produced a progressive concordant increase in V-LA and V-RA intervals (Fig. 2d).

Tachycardia could be initiated by atrial extrastimuli but ventricular premature beats were ineffective. The atrial activation sequence during tachycardia was different from that observed in response to a ventricular extrastimulus at any coupling interval.

Discussion

Four distinct patterns of retrograde conduction were observed in this series of patients. These basic patterns are determined by the relative contribution to atrial activation over the normal and accessory pathways.

(1) Patients in group 1 showed constancy of the ventriculoatrial intervals at all coupling intervals of V_2 as a result of predominant conduction in the accessory pathway (Fig. 2a) (Narula, 1974; Wellens and Durrer, 1974). The small but equal increase in V-RA and V-LA intervals in 1 patient was attributed to intraventricular delay.

(2) Conduction over the accessory pathway predominated at longer coupling intervals of V_2 in patients in group 2. When the V_1-V_2 interval was reduced to within the retrograde effective refractory period of the accessory pathway the sudden increase in V-RA and V-LA intervals and altered atrial activation sequence reflects continued conduction in the normal pathway (Fig. 2b).

(3) Conduction over both the normal and accessory pathways resulting in atrial fusion at long coupling intervals of V_2 was observed in patients in group 3 (Fig. 2c). Conduction in the accessory pathway results in a constant V-LA interval throughout, while delayed conduction in the normal pathway results in a gradual increase of the V-RA interval.

While this delay exceeds the conduction time from the accessory pathway to the right atrium (at the site of recording) the V-RA interval parallels the V-LA interval. In 2 patients the beginning of the V-RA 'plateau' is coincident with the upper limit of the tachycardia zone suggesting that block rather than delay in the normal pathway allowed capture of the right atrium as a result of spread of activation from the accessory pathway.

(4) Atrial fusion was observed at all coupling intervals of V_2 until block in the accessory pathway in patients in group 4 (Fig. 2d and Fig. 7). The gradual increase in the V-RA interval as V_1-V_2 was increased indicates atrial activation as a result of conduction over the normal pathway. In contrast, the V-LA interval remains constant until block occurs in the accessory pathway. Continued conduc-

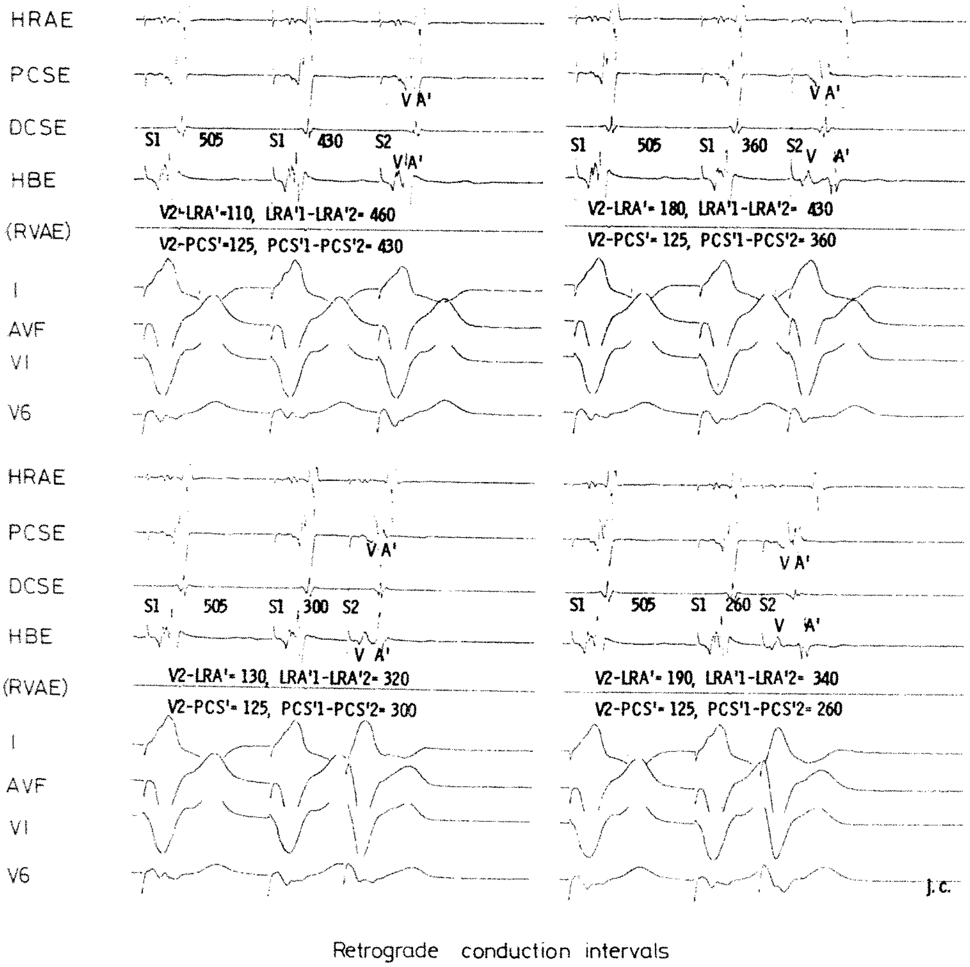
HRAE
PCSE
DCSE
HBE
(RVAE)
I
AVF
V1
V6
S1 505 S1 430 S2
V A'
V2-LRA'=110, LRA'1-LRA'2= 460
V2-PCS'=125, PCS'1-PCS'2= 430
S1 505 S1 360 S2
V A'
V2-LRA'= 180, LRA'1-LRA'2= 430
V2-PCS'= 125, PCS'1-PCS'2= 360
S1 505 S1 300 S2
V A'
V2-LRA'= 130, LRA'1-LRA'2= 320
V2-PCS'= 125, PCS'1-PCS'2= 300
S1 505 S1 260 S2
V A'
V2-LRA'= 190, LRA'1-LRA'2= 340
V2-PCS'= 125, PCS'1-PCS'2= 260
J.C.
Retrograde conduction intervals

Fig. 5 *Programmed ventricular premature stimuli (S_2) at coupling intervals of 430 ms* (upper left*),* *360 ms* (upper right), *300 ms* (lower left), *and 260 ms* (lower right) *in case 3. For discussion see text.*

tion in the normal pathway results in a sudden jump in the V-LA interval associated with a change in atrial activation sequence (Tonkin *et al.*, 1975). Exclusive accessory pathway conduction, therefore, never occurred in this group. Two patients, one from each of group 2 and group 3 showed conduction patterns which appeared to represent a modification of the basic conduction pattern of the group. In case 4 the slight increase in the V-RA interval between coupling intervals of V_2 of between 430 and 300 ms was attributed to intra-atrial delay. The absence of any severe changes in atrial activation sequence throughout the curve (Fig. 3) is not unexpected because the accessory pathway was sited near the atrioventricular node in this patient and conduction in either the normal or accessory pathways may result in similar retrograde activation sequences (Gallagher *et al.*, 1977). However, because the low right atrial electrogram was not clear, the complete atrial activation sequence is not known.

Case 3 had a variation of the basic pattern of group 3 (Fig. 5 and 6). It is postulated that the sudden delay in the right atrial electrogram, sustained over a small range of coupling intervals, is a result of failure of ventriculoatrial conduction in the normal pathway, allowing capture of the right atrium by continued conduction in the accessory pathway. This interpretation is supported by the observation that the V-RA intervals in this zone

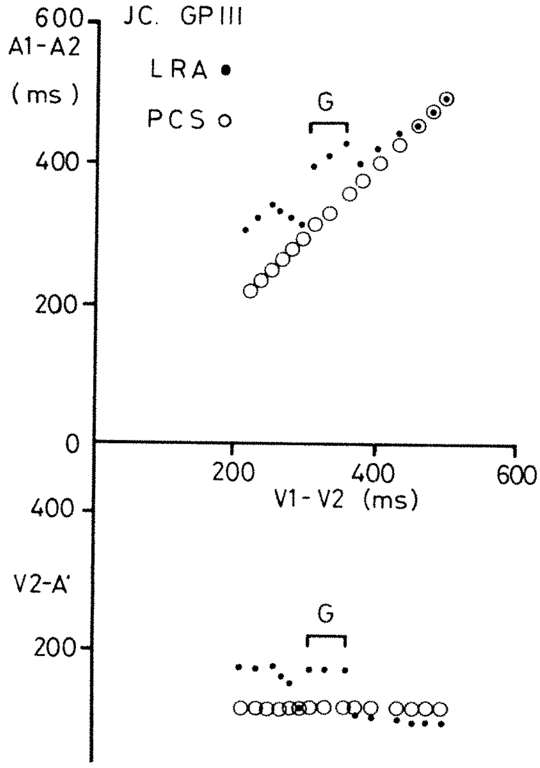

Fig. 6 *Retrograde conduction curve from case 3 (group 3). For discussion see text. G, gap in retrograde His Purkinje/atrioventricular nodal conduction.*

are similar to those seen at short coupling intervals of V_2 when accessory pathway conduction predominates. In effect, there is a gap in ventriculoatrial conduction in the normal pathway (Akhtar *et al.*, 1974) but this gap is concealed by continued conduction in the accessory pathway. A similar case has been described by Wellens (1977).

Svenson *et al.* (1975) studied patterns of ventriculoatrial conduction in patients with overt Wolff-Parkinson-White syndrome and found fusion patterns only in patients with lateral bypass tracts. In the 5 patients in our series with accessory pathways in the region of the distal coronary sinus, atrial fusion was demonstrated at long coupling intervals of V_2, with exclusive accessory pathway conduction at short coupling intervals in 2 patients and exclusive atrioventricular nodal conduction at short coupling intervals in 3 patients. In contrast to the observation of Svenson *et al.* (1975) we showed atrial fusion patterns in 3 of the 7 patients with proximally located bypass tracts, 2 of whom showed exclusive bypass tract conduction only at short coupling intervals of V_2. Of the other 4 patients with proximally located pathways, 2 disclosed predominant accessory pathway conduction throughout (group 1) and 2 had the pattern typical of group 2.

Of the 5 patients with short PR intervals, 4 patients had atrial fusion patterns at long coupling intervals of V_2 and 1 patient showed exclusive accessory pathway conduction throughout. Retrograde conduction in an atrionodal pathway may result in earliest atrial activation in the region of the proximal coronary sinus (Camm *et al.*, 1978). In 2 patients this possibility was excluded by the finding of earliest atrial activity in the distal coronary sinus electrogram. In the 3 other patients with proximally situated bypass tracts a ventricular premature stimulus delivered at the time of the His bundle potential resulted in exact atrial capture. This observation excludes retrograde conduction in an atrionodal pathway (Ward *et al.*, 1978) and confirms ventriculoatrial conduction in a direct ventriculoatrial connection (Coumel and Attuel, 1974; Zipes *et al.*, 1974; Neuss *et al.*, 1975; Sellers *et al.*, 1976).

Tachycardia could not be initiated by a ventricular premature beat in any patient in whom there was evidence of normal pathway ventriculoatrial conduction at all coupling intervals of V_2 (group 2 and group 4). It is suggested that re-entry towards the ventricles over the atrioventricular node-His pathway was prevented by continued retrograde conduction in this pathway. Ventricular premature beats were effective in initiating tachycardia in 2 of the 4 patients who showed exclusive accessory pathway conduction only at short coupling intervals (group 3). In these patients, the upper limit of the

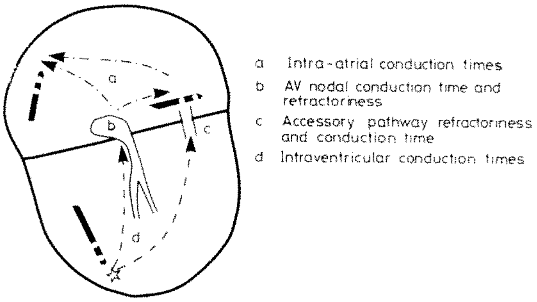
a
b
c
d
a Intra-atrial conduction times
b AV nodal conduction time and refractoriness
c Accessory pathway refractoriness and conduction time
d Intraventricular conduction times

Fig. 7 *Determinants of retrograde conduction patterns during right ventricular extrastimulation in patients with accessory bypass tracts. The pattern of atrial activation is determined by the relative conduction times from the site of stimulation to the site of recording in both the normal and abnormal pathways and the state of refractoriness in these pathways.*

tachycardia zone coincided with the upper limit of the V-RA interval plateau. The inability of ventricular premature beats to initiate tachycardia in the other 2 patients in group 3 may be related to concealed retrograde invasion of the normal pathway at short coupling intervals (Wellens, 1977). These observations are similar to those made by Sung *et al.* (1977a) in patients with overt type A Wolff-Parkinson-White syndrome.

In the absence of accessory ventriculoatrial connections, atrial activation during ventricular pacing begins close to the atrioventricular node and spreads to more distant points (Amat-y-Leon *et al.*, 1976; Gallagher *et al.*, 1977). The relative timing of atrial activation at different sites is determined by intra-atrial conduction times to the sites of recording. When two or more ventriculoatrial pathways are present the atrial activation patterns depends on the relative contribution to atrial depolarisation by each conduction pathway. The presence of two or more concealed ventriculoatrial accessory pathways may make interpretation difficult especially if these pathways have similar characteristics and location. Several determinants may interact to produce any given activation pattern (Fig. 7). Though we have seen 4 basic patterns of ventriculoatrial conduction in patients with concealed accessory pathways, other varieties may occur. For example, atrial fusion at all coupling intervals of V_2 was reported by Sung *et al.* (1977a) in 3 of 29 patients with type A Wolff-Parkinson-White syndrome. The presence of intra-atrial or intraventricular delay or gaps in ventriculoatrial conduction in the normal pathway (Akhtar *et al.*, 1974) or accessory pathway may result in variations of basic patterns. In addition, the basic pattern may be modified by changes in the ventricular driving rate.

Retrograde atrial activation patterns may be important in the diagnosis and location of concealed accessory pathways especially in those patients in whom it may not be possible to initiate tachycardia at electrophysiological study. It is clear that constancy of the ventriculoatrial interval is, by itself, an inadequate criterion for the diagnosis of concealed ventriculoatrial pathways. If the V-RA interval is considered, a progressive increase was shown in 8 patients (group 3 and group 4) and a sudden increase in 2 patients one of whom had intra-atrial delay. In the absence of left atrial recordings these V-RA patterns may have been reasonably attributed to conduction in the normal pathway alone. For this reason, it is important that atrial activity should be recorded from sites closely adjacent to both normal and accessory pathways.

Recently it has been re-emphasised that concealed accessory pathways may in fact be the anatomical substrate for tachycardias previously diagnosed as depending on intranodal re-entry (Barold and Coumel, 1977; Sung *et al.*, 1977b; Pritchett *et al.*, 1978). The distinction between these mechanisms is clearly of therapeutic importance particularly if surgical intervention is considered.

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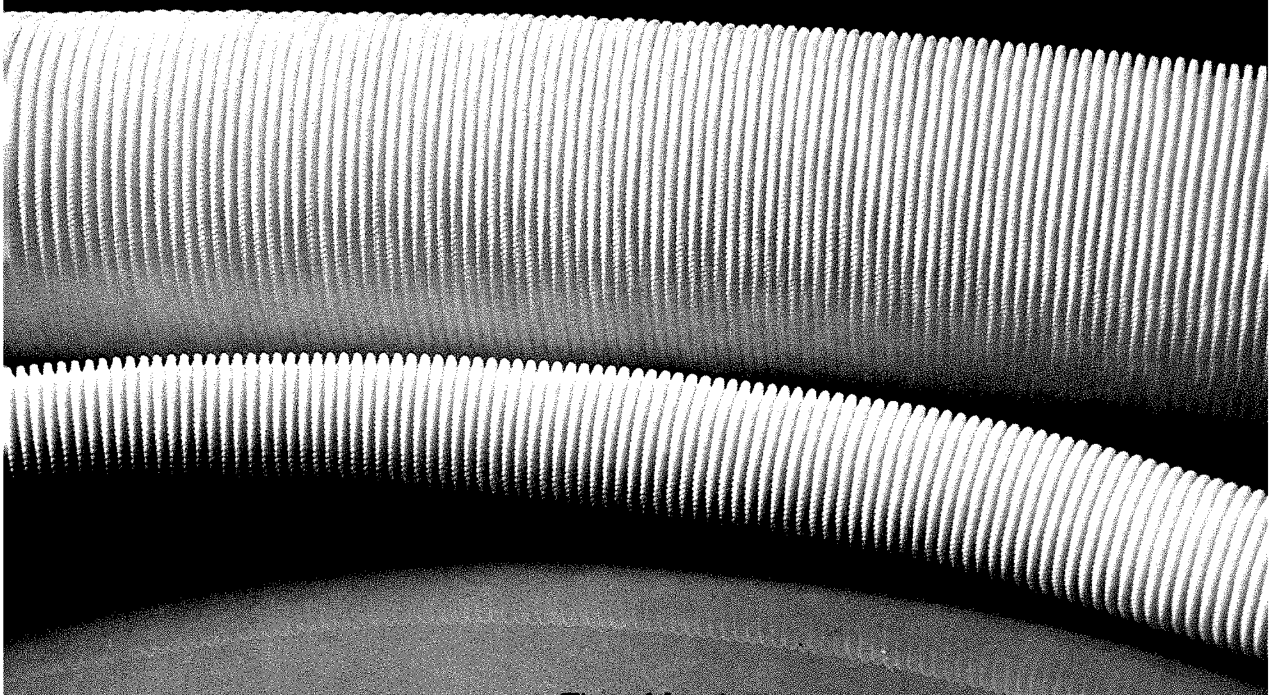

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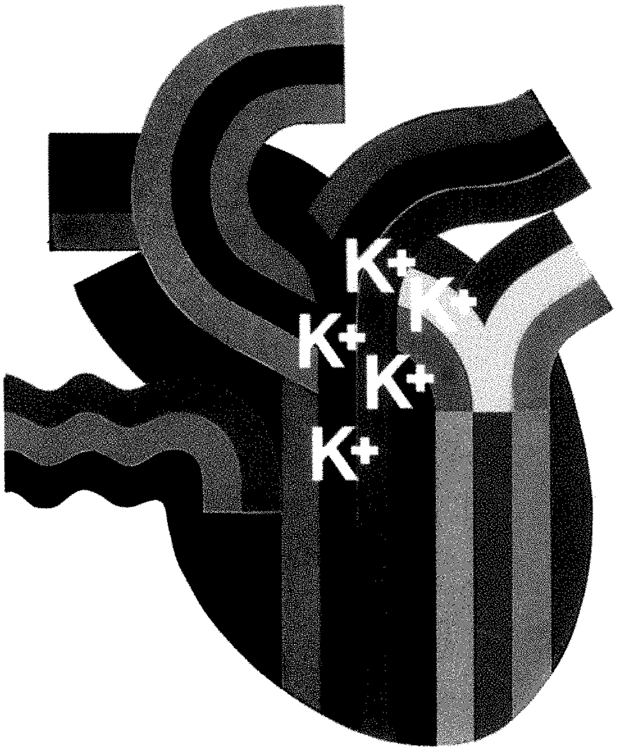

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British Heart Journal, 1979, **42,** 201-204

Q wave T wave vector discordance in hypertrophic cardiomyopathy: septal hypertrophy and strain pattern

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SUMMARY Hypertrophic cardiomyopathy is a common cause of prominent non-infarctional Q waves. A retrospective analysis of previously published cases confirmed a characteristic Q wave T wave vector discordance in hypertrophic cardiomyopathy. In 41 of 44 cases with predominant Q waves (as part of QS or Qr complexes where Q wave amplitude exceeded R wave height), the T wave was positive, and in all cases with QS type complexes the T wave was positive. This characteristic electrocardiographic sign probably represents a pattern of septal hypertrophy and strain (Q waves with positive T waves and ST segment elevation) which is the inverse of the classical pattern of left ventricular hypertrophy and strain (tall R waves with inverted T waves and ST segment depression).

Hypertrophic cardiomyopathy, including the classic syndrome of idiopathic hypertrophic subaortic stenosis, is an important cause of pseudoinfarct electrocardiographic patterns (Estes *et al.*, 1963; Braudo *et al.*, 1964). Q waves simulating myocardial infarction may appear in multiple leads, mimicking anteroseptal, anterolateral, and/or inferior wall injury. In addition, tall R waves in the right chest leads may lead to the mistaken diagnosis of true posterior myocardial infarction (Goldberger, 1975). In Frank and Braunwald's (1968) series of patients with classic idiopathic hypertrophic subaortic stenosis, pseudoinfarct Q waves were noted in 56 per cent of 123 cases.

Although the high prevalence of non-infarct Q waves in hypertrophic cardiomyopathy is widely known, criteria for distinguishing these patterns from actual infarction have received only limited attention. The morphology of the Q waves may be of some diagnostic help. The Q waves of hypertrophic cardiomyopathy may show a relatively distinctive, lance-like appearance, with a narrow, deep, and sharply inscribed contour. In other cases, the Q waves have a jagged, W-shaped morphology (Fig. 1). While such Q wave patterns may be suggestive of hypertrophic cardiomyopathy, particularly in younger patients, these patterns are by no means diagnostic. Deep, narrow Q waves are commonly seen with Duchenne muscular dystrophy (Perloff *et al.*, 1966) and bizarre QS complexes may occur with myocardial infarction or other types of cardiomyopathy. Furthermore, the abnormal initial depolarisation forces seen in the vectorcardiogram in cases of hypertrophic cardiomyopathy are generally indistinguishable from true infarct patterns (Estes *et al.*, 1963; Stein *et al.*, 1968).

In certain cases, the polarity of the T wave may be of additional help in the differential diagnosis of hypertrophic cardiomyopathy *vs.* myocardial infarction. It has been observed that the T wave vector in hypertrophic cardiomyopathy is characteristically oriented away from the direction of the Q wave vector (Goldberger, 1975). As a result, leads showing predominant Q waves, as part of QS or Qr type complexes, will show positive T waves. In contrast, infarct Q waves are often associated with negative T waves, reflecting primary ischaemic repolarisation abnormalities. The purpose of this study was to investigate further the validity of the discordant Q wave T wave sign in hypertrophic cardiomyopathy and to discuss the concept of a 'septal hypertrophy and strain' pattern.

Methods

The electrocardiograms of patients with hypertrophic cardiomyopathy documented primarily by catheterisation were reviewed in a retrospective fashion. Forty-four cases of hypertrophic cardiomyopathy with deep pseudoinfarct Q waves were

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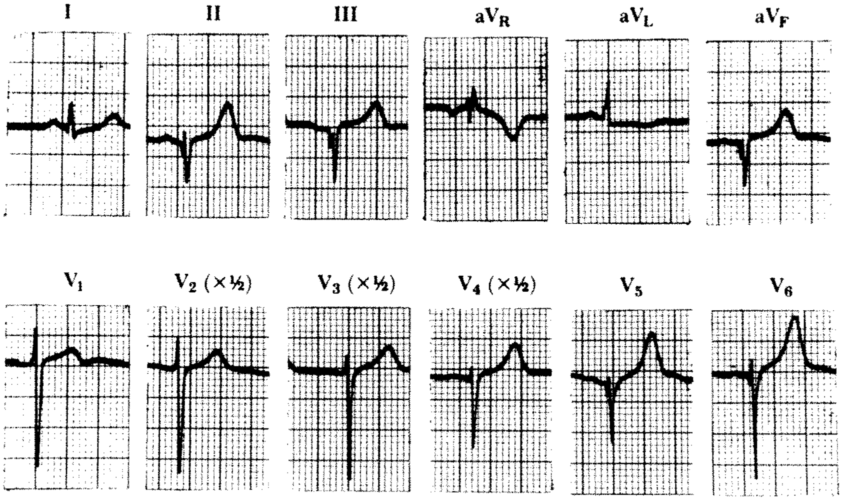

Fig. 1 *Note positive T waves, with slight ST segment elevation in leads with predominant Q waves, as part of QS or Qr type complexes (III, aVF), as well as in W shaped complexes (II, V4 to V6).*

found among the published reports[1]. These electrocardiograms were evaluated specifically to test the hypothesis that the T waves would be positive in leads showing predominant Q waves, as part of QS or Qr type complexes. Q wave patterns meeting these criteria in one or more of leads I, II, aVL, aVF, V2 to V6 were studied.

Results

In 41 of 44 cases (93%), all leads showing predominant Q waves (QS or Qr complexes) also had positive T waves. Furthermore, *all* leads showing QS or W shaped complexes had positive T waves. Two partial exceptions to this Q wave T wave discordance pattern were noted. In 1 case reported by Leachman and Leatherman (1965, Fig. 2), the electrocardiogram showed an atypical intraventricular conduction delay with QS waves in leads I and II, and Qr waves in leads V5 to V6, all associated with positive T waves. However, lead aVL showed a Qr complex with slight T wave inversion. In another case (Morgan and Forker, 1972, case 10), an incomplete right bundle-branch block was present, and not all of the leads with Qr type complexes showed positive T waves. Finally, Flowers and Horan (1973) also reported a case with prominent Q waves (as part of QR complexes) and inverted T waves.

It should be emphasised that this discordant Q wave T wave sign applies only in leads showing *predominant* Q waves (QS or Qr patterns where the Q wave exceeds the R wave amplitude). In cases where QR complexes are present, with the R wave equalling or exceeding the Q wave, the T wave may be upright or inverted. Fig. 1 shows a typical example of Q wave T wave discordance in leads with predominant Q waves.

Discussion

The Q waves in hypertrophic cardiomyopathy probably represent augmented depolarisation forces from the hypertrophied septum (Braudo *et al.*, 1964). Normally, the left-to-right direction of septal

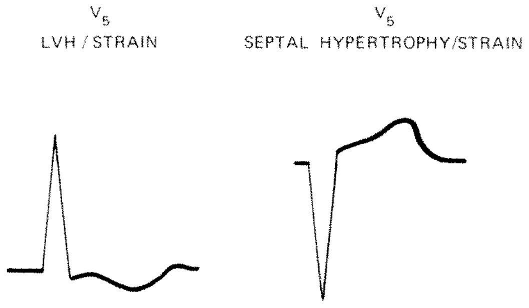

Fig. 2 *Classical left ventricular hypertrophy and strain pattern (ST segment depression with inverted T waves in leads with prominent R waves) is the inverse of septal hypertrophy and strain pattern (positive T waves with slight ST segment elevation in leads with predominant Q waves, for example V5).*

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[1] Hollman *et al.*, 1960 (1); Benchimol *et al.*, 1963 (1); Estes *et al.*, 1963 (1); Prescott *et al.*, 1963 (3); Braudo *et al.*, 1964 (6); Cohen *et al.*, 1964 (1); Welch and Scott, 1965 (1); Coyne, 1968 (3); Frank and Braunwald, 1968 (3); Klein *et al.*, 1968 (3); Leachman and Leatherman, 1968 (3); Peter *et al.*, 1968 (2); Stein *et al.*, 1968 (1);Bahl *et al.*, 1970 (1); Marriott, 1972 (1); Morgan and Forker, 1972 (2);Flowers and Horan, 1973 (1); Chung, 1974 (2); Goldberger, 1975 (5); Hansen *et al.*, 1975 (1); Witham, 1975 (1); Friedman, 1977 (1).

depolarisation produces small positive (r) waves in the right chest leads, and small septal q waves in the left chest leads and one or more of the limb leads. Septal hypertrophy may magnify these q waves, resulting in inferior and/or anterior pseudo-infarct Q wave patterns. In some cases of hypertrophic cardiomyopathy, QS waves may appear in the right praecordial leads (V1 to V3), simulating anteroseptal myocardial infarction. It is not certain whether the Q waves in these leads reflect posteriorly directed septal forces (Wigle and Baron, 1966) or whether they are the result of concomitant hypertrophy of the left ventricular free wall. Coyne (1968) suggested that the abnormal depolarisation forces in hypertrophic cardiomyopathy might also result from an alteration in the normal sequence of ventricular activation.

The characteristic Q wave T wave vector discordance in hypertrophic cardiomyopathy can be explained by analogy with the QRS-T pattern seen with classical left ventricular hypertrophy. The electrocardiographic pattern of concentric or free wall left ventricular hypertrophy generally shows discordant QRS and T wave vectors: leads with tall R waves are associated with T wave inversions, as part of the left ventricular hypertrophy and 'strain' pattern (Fig. 2). It is not certain whether these 'strain' T waves reflect primary left ventricular ischaemia or whether they are secondary to an alteration in the repolarisation sequence of hypertrophied muscle.

In cases of predominant septal hypertrophy, an analogous septal 'strain' pattern might occur. However, since septal depolarisation is oriented to the right, the septal hypertrophy and strain pattern (deep Q waves and positive T waves) seen in the lateral chest leads will be the inverse of the classical free wall left ventricular hypertrophy and strain pattern (tall R waves with T wave inversions) (Fig. 2). In addition, these deep septal Q waves are often followed by ST segment elevation, reciprocal to the ST segment depression typically seen with left ventricular hypertrophy and strain.

With myocardial infarction, leads showing prominent Q waves may also have positive T waves. However, in many cases, distinctive ischaemic T wave inversions will appear. The presence of predominant Q waves (as part of QS or Qr type complexes) with negative T waves makes the diagnosis of pure hypertrophic cardiomyopathy unlikely. On the other hand, the presence of deep Q waves (particularly with a lancet or W shape) with positive T waves is compatible with, but not diagnostic of, hypertrophic cardiomyopathy.

In some cases, hypertrophic cardiomyopathy and coronary artery disease may co-exist. However, the effect of transmural infarction on the pseudo-infarct electrocardiographic patterns of hypertrophic cardiomyopathy has not been specifically described. In cases of hypertrophic cardiomyopathy with deep Q waves, acute myocardial infarction might have different effects, depending on the location of the infarct. For example, septal infarction might lead to a paradoxical diminution in Q wave magnitude, since the Q waves reflect septal enlargement. Lateral infarction, on the other hand, should augment these septal Q waves, because of loss of counterbalancing free wall depolarisation forces. Acute myocardial infarction superimposed on the pattern of hypertrophic cardiomyopathy might also produce diagnostic ischaemic repolarisation changes.

Discordance of the Q wave T wave vector may thus be a helpful clue in the differential diagnosis of hypertrophic cardiomyopathy. The positive T waves in leads with predominant Q waves (as part of QS or Qr complexes) probably represent a pattern of septal hypertrophy and strain.

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Assessment of left ventricular performance and myocardial viability using quantitative radioisotope techniques

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SUMMARY The diagnostic value of a combined radionuclide technique was compared with conventional angiocardiographic techniques in 60 patients with coronary artery disease. Quantitative ^{201}Tl myocardial imaging combined with radionuclide angiocardiography using ^{99m}Tc-HSA provided a safe and accurate method for the assessment of left ventricular performance. The defects on the ^{201}Tl images correlated with the severity of asynergy seen on the contrast ventriculogram. Static imaging alone distinguished hypokinetic from akinetic or dyskinetic areas. However, using both tracer techniques, akinesis could be distinguished from dyskinesis. In patients with disturbed left ventricular function, cardiac transit times correlated with haemodynamic changes, and left ventricular ejection fraction was the most sensitive index. Thus, this combined radionuclide approach provides data for the evaluation of overall and regional wall function. A major advantage of this non-invasive quantitative technique is its applicability to the critically ill patient at the bedside.

Over the past decade coronary angiography and left ventriculography have become essential investigations in the assessment of patients with coronary artery disease. Recent developments of new techniques employing radioactive isotopes in the evaluation of cardiac function suggest that information, previously available only at cardiac catheterisation, can now be obtained non-invasively (Hurley *et al.*, 1971; Gorton, 1972; Pachinger *et al.*, 1973; Zaret *et al.*, 1973; Felix *et al.*, 1975; Feller and Sodd, 1975; Lebowitz *et al.*, 1975; Strauss *et al.*, 1975; Wackers *et al.*, 1975; Büll *et al.*, 1976). Radionuclide imaging still requires further assessment and verification before being accepted as an effective means of delineating the extent of myocardial disease and the level of cardiac chamber performance in patients with ischaemic heart disease. The purpose of this paper is to examine the value of a combined radionuclide approach, compared with contrast angiocardiographic techniques.

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Patients and methods

Sixty patients (average age 42 years, range 28 to 65) with suspected coronary artery disease were examined by both contrast angiocardiographic techniques and a combined radionuclide study using static imaging with ^{201}Tl and dynamic radionuclide angiocardiography with ^{99m}Tc-human serum albumin (^{99m}Tc-HSA).

RADIONUCLIDE STUDY

Myocardial perfusion imaging was performed after an intravenous injection of 2 mCi ionic ^{201}thallium (thallium chloride, Duphar Co., Petten, The Netherlands) with a high resolution scintillation camera (Phogamma HP, Searle Incorporation) using a high resolution, low energy, parallel hole collimator with a 25 per cent window set symmetrically around the 80 keV x-ray peak of the element. Images were obtained in the 45° right anterior oblique, anterior, 60° left anterior oblique, and lateral projections, beginning with the first image 15 minutes after intravenous injection of the tracer;

250 K counts were stored for each image, and were further processed by scintigraphic analyser system (5407 HP). The scintigrams were normalised for gamma camera field non-uniformity; correction for non-cardiac background was made by subtracting the average counts per matrix element of a representative region of interest (ROI) in the upper anterior mediastinum from the total image. A 9-point smoothing procedure was then applied. In order to allow for the effect of changing blood background during the course of the examination, the individual image was always recorded at the same time interval after the intravenous injection (right anterior oblique 15 minutes, anterior 20 minutes, left anterior oblique 25 minutes, and lateral 30 minutes, after the injection of the tracer).

The thallium images were evaluated in the following way.

(1) The location of the perfusion defect was determined and its size outlined and expressed as a percentage of the total cardiac image in each projection.

(2) The average count rates determined in areas with diminished or absent uptake of ^{201}Tl were expressed as a percentage of the average counts observed in regions with scintigraphically intact myocardium.

(3) For quantification of ^{201}Tl uptake by the myocardium the scintigrams were divided into 5 count levels expressed as a percentage of maximum uptake (0 to 20%, 20 to 40%, 40 to 60%, 60 to 80%, and 80 to 100%). The ^{201}Tl uptake of each count level was also expressed as the percentage of myocardial counts to recorded background counts in the reference area in the upper anterior mediastinum, which was taken as representative of blood background.

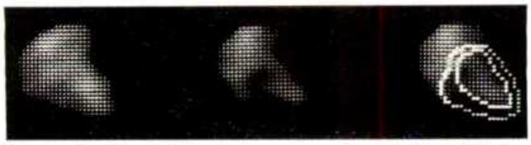

Fig. 1 *Radionuclide angiography using ^{99m}Tc-HSA in a patient with normal left ventricular function. The passage of the bolus is recorded in right anterior oblique 30° projection; end-diastolic and end-systolic images are outlined with a light pen and are then superimposed for the study of regional wall motion.*

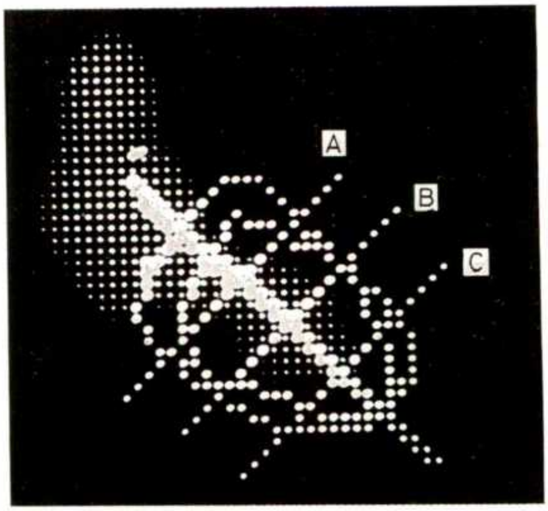

Fig. 2 *Profile scanning of the end-diastolic and end-systolic images in the major length axis and in 3 axes at right-angles (A, B, C) corresponding to those measured in the angiographic techniques.*

After completion of the myocardial perfusion study, 15 mCi ^{99m}Tc-HSA were injected intravenously and, using the first bolus transit, left ventricular ejection fraction (LVEF) was computed from the usual mathematical formulae (Van Dyke *et al.*, 1972; Weber *et al.*, 1972; Ashburn *et al.*, 1973). The passage of the bolus was recorded in the 30° right anterior oblique projection and stored in list mode on the magnetic disc of the scintigraphic analyser. Background correction was made from a semicircular region of interest around the apex and the anterior wall of the left ventricle (Van Dyke *et al.*, 1972). From selected ROIs (right atrium, right ventricle, lung, and left ventricle) time activity histograms in low frequency mode (time interval 1 second) and in high frequency mode (time interval 50 milliseconds) were recorded.

Transit times (left ventricular mean transit time, pulmonary mean transit time, left ventricular minimal transit time) were calculated from the low frequency histograms after correction for recirculation. The high frequency histograms were used for the determination of LVEF after correction for the time count loss and non-cardiac background

Table 1 *Data in 60 patients with 72 asynergic segments*

^{201}*Tl images % defect (in view with maximum defect)*	*Wall motion on contrast ventriculogram (numbers of patients)*			
None	Normokinesis	(10)		
0–10%	Hypokinesis	(14)		
10–20%	Hypokinesis	(11)		
20–30%	Akinesis	(24),	dyskinesis	(4),
			hypokinesis	(3)
> 30%	Akinesis	(10),	dyskinesis	(6)
*Mean values of % defect**				
18 ± 9%	Hypokinesis	(28)		
30 ± 12%	Akinesis	(34)		
35 ± 9%	Dyskinesis	(10)		

* Differences between hypokinesis and akinesis or dyskinesis were significant ($P < 0{\cdot}01$).

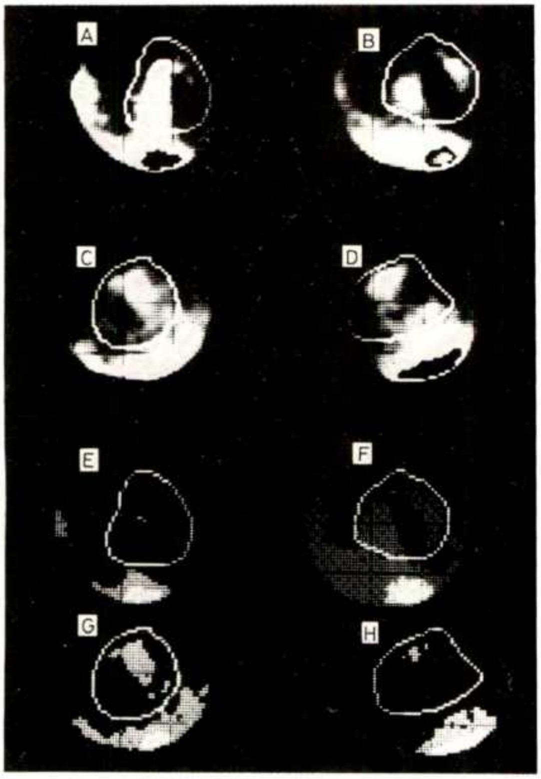

Fig. 3 *Patient with anteroseptal myocardial infarction. (A–D) Digitised ^{201}Tl scintigrams in right anterior oblique, anterior, left anterior oblique, and lateral views, respectively. (E–H) Corresponding views displayed as 5 different count levels (0 to 20, 20 to 40, 40 to 60, 60 to 80, and 80 to 100% of maximum ^{201}Tl uptake).*

contribution. For left ventricular wall motion analysis 4 to 6 selected end-diastolic and end-systolic frames from the early downslope part of the time activity histogram were summed up to create one representative end-diastolic and end-systolic image. These images were outlined with a light pen on the TV screen of the scintigraphic analyser and, by precise superimposition, we attempted to identify regional asynergy (Fig. 1). By subtraction of the end-systolic from the end-diastolic image, the regional distribution of stroke volume was visualised.

The ratio of the length of the end-systolic to the end-diastolic perimeter of the left ventricular circumference was computed from both radionuclide and contrast ventriculograms to obtain

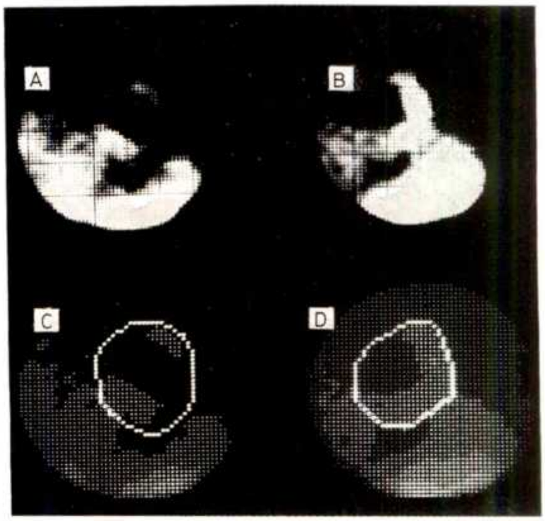

Fig. 4 *Patient with extensive anteroseptal infarction. (A, B) Digitised ^{201}Tl scintigrams in the anterior and left anterior oblique projections. (C, D) Five different count levels (as in Fig. 3). Note the defect in anterior wall which corresponds to 20 to 40 per cent of maximum ^{201}Tl uptake.*

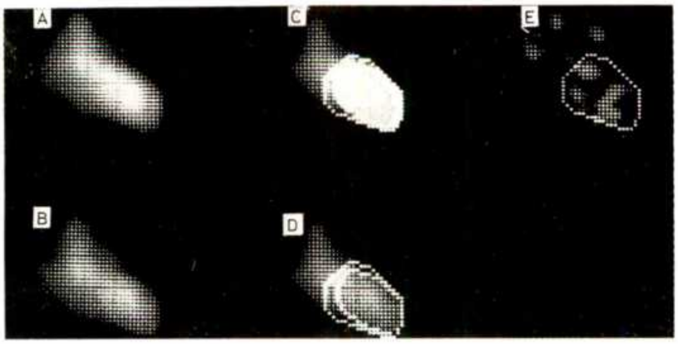

Fig. 5 *Radionuclide angiography (RAO 30°) in same patient as Fig. 4 shows akinesis of anteroapical wall segments. (C D) Superimposed end-diastolic and end-systolic images. (E) Regional distribution of stroke volume.*

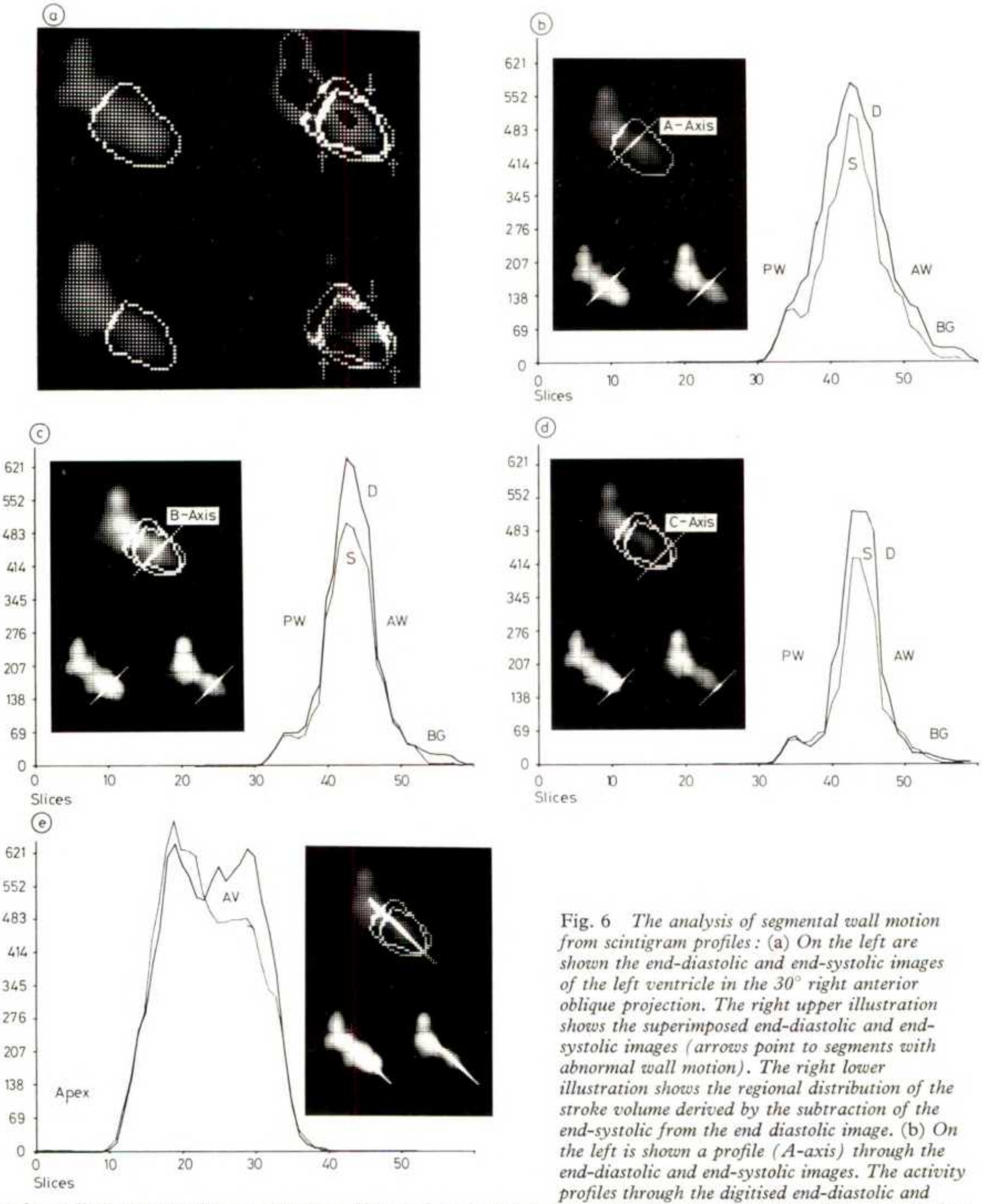

Fig. 6 *The analysis of segmental wall motion from scintigram profiles:* (a) *On the left are shown the end-diastolic and end-systolic images of the left ventricle in the 30° right anterior oblique projection. The right upper illustration shows the superimposed end-diastolic and end-systolic images (arrows point to segments with abnormal wall motion). The right lower illustration shows the regional distribution of the stroke volume derived by the subtraction of the end-systolic from the end diastolic image.* (b) *On the left is shown a profile (A-axis) through the end-diastolic and end-systolic images. The activity profiles through the digitised end-diastolic and end-systolic images are shown on the right. The good separation of the two profiles reflects normal wall motion.* (c) *The superimposed end-diastolic and end-systolic images show abnormal motion in the mid anterior wall and diaphragmatic segment (left). The B axis profiles show akinesis in both regions (right).* (d) *Superimposed images and C-axis scan profiles.* (e) *Superimposed images and major length axis scan profiles. (S, systole; D, diastole; PW, posterior wall; AW, anterior wall; BG background; AV, aortic valve.)*

comparable indices representative of ventricular wall motion. To analyse regional wall motion quantitatively, we obtained scan profiles from the end-diastolic and end-systolic images by measurement of the major length axis (L) and 3 axes at right-angles (A, B, C), as in the angiographic technique (Fig. 2).

HAEMODYNAMIC AND ANGIOCARDIOGRAPHIC STUDIES

Haemodynamic studies included complete right and left heart catheterisation followed by biplane

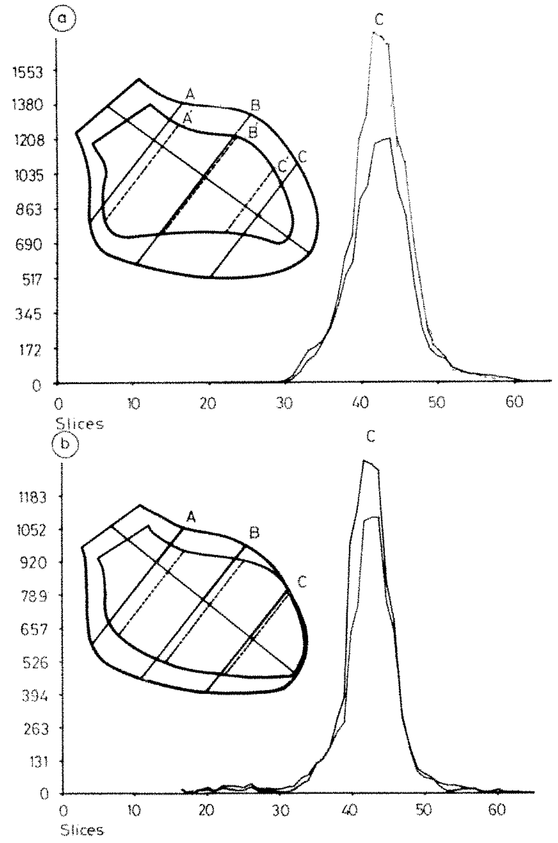

Fig. 7 *Quantitative analysis of regional wall motion on contrast ventriculogram and corresponding profiles on radionuclide ventriculogram.* (a) *On the left are shown axes A, B, C of the contrast ventriculogram; on the right, the corresponding profiles along the C axis of the radionuclide ventriculogram. Both methods show good wall motion.* (b) *A patient with akinesis of anteroapical wall segment. On the left are shown axes A, B, C of the contrast ventriculogram; on the right, the lack of difference between systolic and diastolic C axis profiles indicates akinesis.*

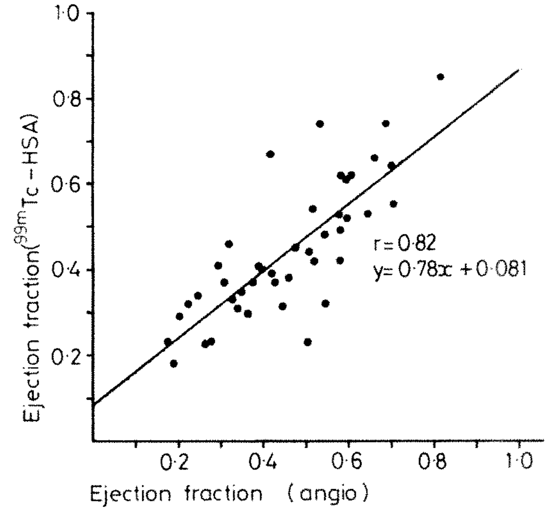

Fig. 8 *Correlation between radionuclide and cineventriculographic measurement of ejection fraction in 45 patients.*

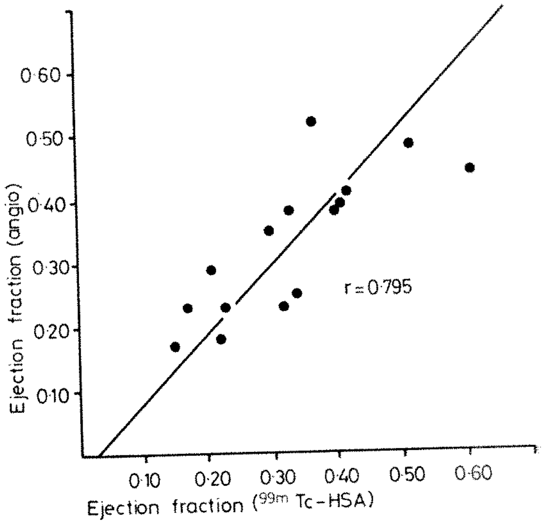

Fig. 9 *Correlation between radionuclide and cineventriculographic measurement of ejection fraction in 15 patients with left ventricular aneurysm.*

cineventriculography and selective coronary arteriography. Left ventricular ejection fraction was calculated using the area-length method (Dodge *et al.*, 1960). Regional wall motion abnormalities were analysed quantitatively by measuring the percentage systolic shortening along the 6 hemi-axes and the major length axis.

Radionuclide data were computed without knowledge of the contrast ventriculographic data. Statistical analysis used standard formulae for regression analysis and Student's paired t test.

Results

The results of the analysis of ^{201}Tl images in the 60 patients are summarised in Table 1. Ten patients showed homogeneous ^{201}Tl uptake without significant perfusion defects. All these patients showed normal wall motion on the contrast ventriculogram. In the remaining 50 patients, 72 asynergic segments were observed. Though there was some overlap, there were significant differences between the sizes of the scintigraphic defects when there were akinetic or dyskinetic areas and when there were hypokinetic zones ($P < 0{\cdot}01$). However, it was not possible to separate akinetic from dyskinetic zones by static thallium imaging.

Fig. 3 shows quantitative ^{201}Tl scintigrams in a patient with anteroseptal myocardial infarction. In all patients, the location of the area with reduced ^{201}Tl uptake corresponded to abnormal wall motion on the dynamic radionuclide study. Fig. 4 shows a patient with an extensive anteroseptal myocardial infarct; the ^{201}Tl defect corresponds to anteroseptal akinesis on the radionuclide angiogram (Fig. 5).

Detailed analysis of segmental wall motion was attempted from scintigram profiles of end-diastolic and end-systolic images, as shown in Fig. 6 a–e. After superimposition, good separation of the diastolic and systolic profiles indicates normal wall motion, while a lack of difference between the two indicates akinesis; there is dyskinesis when the systolic profile exceeds the diastolic profile. The profiles were compared with the corresponding axes (A, B, C) of the contrast ventriculogram (Fig. 7a, b).

Fig. 8 shows the correlation between the ejection fraction obtained by the angiocardiographic method and that obtained by the isotope method in a group of 45 patients. None of these patients had ventricular aneurysms. In order to evaluate the sensitivity of this radionuclide technique in detecting regional dyskinesis, we examined 15 patients with angiographically proven anteroapical dyskinesis by both methods. Qualitatively, there was good agreement in 12 cases, but in 3 patients there were discrepancies. Fig. 9 illustrates the correlation between the angiocardiographic and radionuclide ejection fractions in these patients. Though the correlation is statistically significant, it is less good than in a group of patients without dyskinesis. The perimeter index (ratio of end-systolic circumference/end-diastolic circumference) was obtained by both methods; the correlation coefficient in these 15 patients was 0·72.

Fig. 10 shows the advantage of combining static

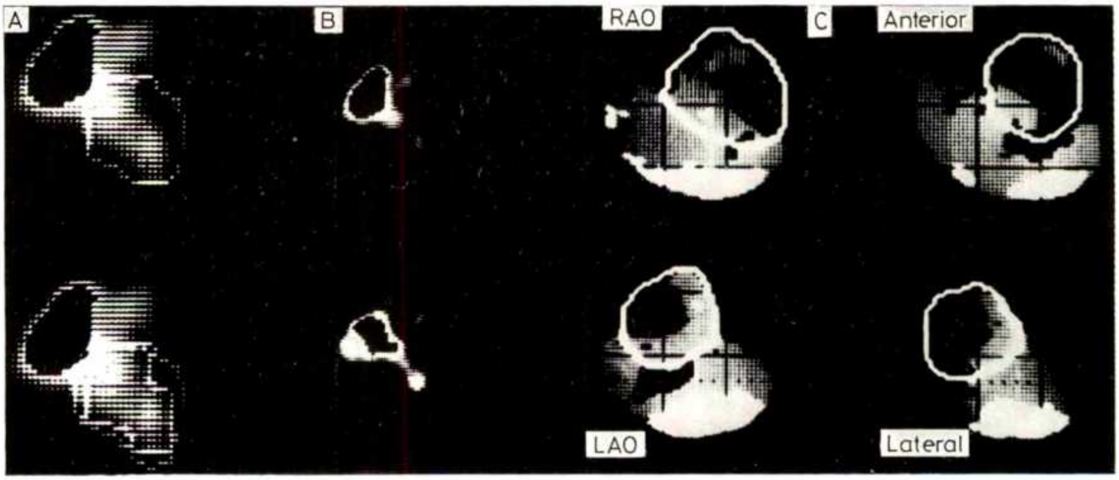

Fig. 10 *Aneurysm of the anteroapical wall verified by cineventriculography. (A) The radionuclide angiocardiogram shows dyskinesis as shown by the superimposed end-systolic and end-diastolic images. (B) By raising the lowest level of counts per unit time which are displayed, stagnation of blood in the aneurysm is shown (as can be shown by cineventriculography). (C) The* ^{201}*Tl scan shows an anteroseptal defect.*

Table 2 *Haemodynamic, angiocardiographic, and radionuclide data in patients with inferior myocardial infarction (group 1), in patients with anteroseptal myocardial infarction (group 2), and in normal control subjects*

	Normal *(n = 13)*	*Group 1* *(n = 8)*	*Group 2* *(n = 14)*
PA (mmHg)	14·0 ±3·0	15·0 ±3·0	27·0 ±12·0*
LVEDP (mmHg)	10·2 ±2·6	14·7 ±3·2	25·2 ±8·0*
EF (angio) (%)	63·0 ±6·0	49·0 ±8·0*	35·0 ±12·0*
VCF (c/s)	1·2 ±0·2	0·9 ±0·2	0·6 ±0·3*
Mean TTL	13·9 ±1·5	16·0 ±4·8	21·2 ±7·0*
Minimal TTLV	5·5 ±0·9	5·6 ±2·0	7·8 ±2·3
Mean TTLV	14·9 ±3·0	15·0 ±1·4*	21·3 ±6·0*
EF(^{99m}Tc-HSA)	62·0 ±10·0	40·0 ±6·0*	37·0 ±12·0*

PA, pulmonary artery mean pressure; LVEDP, left ventricular end-diastolic pressure; EF (angio), left ventricular ejection fraction determined by cineventriculography; VCF, mean circumferential fibre shortening; Mean TTL, mean pulmonary transit time; Minimal TTLV, minimal left ventricular transit time; Mean TTLV, mean left ventricular transit time; EF(^{99m}Tc-HSA), left ventricular ejection fraction measured with ^{99m}Tc-HSA.
* Statistically significant difference from control ($P < 0·05$).

and dynamic imaging. The perfusion defect seen on the thallium scintigram can be correlated with the functional state of this segment; if a wall motion abnormality is observed on the radionuclide angiocardiogram, the perfusion of that segment can be evaluated on the ^{201}Tl scintigram.

Haemodynamic, angiocardiographic, and radionuclide data in patients with inferior myocardial infarction (group 1), in those with anteroseptal myocardial infarction (group 2), and in normal control subjects are shown in Table 2. Haemodynamic measurements were not able to separate group 1 from the control group. However, the ejection fraction, determined by either contrast angiocardiography or by the radionuclide method, differed significantly from normal in both groups ($P < 0·01$). In patients with less severe myocardial damage, the ejection fraction was the most sensitive index of disturbed left ventricular function; in group 2, there was a significant correlation between haemodynamic and radionuclide data. The correlation coefficient (r) between the increased pulmonary arterial pressure and the increased mean pulmonary transit time was 0·70 ($P < 0·05$), and the correlation between ventricular mean transit time and left ventricular end-diastolic pressure was 0·69.

Discussion

Myocardial imaging with diffusible indicators offers the prospect of non-invasive assessment of myocardial perfusion. ^{201}Tl is currently the best of these indicators because of its favourable physical and biological properties (Bradley-Moore *et al.*, 1975; Feller and Sodd, 1975; Lebowitz *et al.*, 1975). The reliability and limitations of thallium scintigrams have been assessed by many authors (Strauss *et al.*, 1975; Wackers *et al.*, 1975; Bailey *et al.*, 1976; Mueller *et al.*, 1976; Pachinger *et al.*, 1977; Wackers *et al.*, 1976). Most of these reports deal with a qualitative correlation between ^{201}Tl-imaging and conventional contrast angiocardiographic techniques. In the present study, attempts were made to measure the perfusion defects on the thallium scan and to correlate them with ventricular function. A good correlation was found between regional Tl-uptake and regional asynergy; thus, quantitative Tl-imaging can partly indicate the severity of ventricular dysfunction. Rigo *et al.* (1975) and Zaret *et al.* (1975) showed a similar relation using potassium-43 imaging in patients with myocardial infarction. We found that the combined use of both tracer techniques, static and dynamic imaging, gives additional information about regional wall function (Pitt and Strauss, 1977).

Radionuclide angiocardiography with ^{99m}Tc pertechnetate of ^{99m}Tc-HSA, using a single intravenous injection of radionuclide and a scintillation camera in combination with a computer system, is an established method for the non-invasive evaluation of left ventricular function (Van Dyke *et al.*, 1972; Weber *et al.*, 1972; Ashburn *et al.*, 1973). Using the first pass method, ejection fraction can be determined with an accuracy comparable with contrast angiocardiographic techniques (Ashburn *et al.*, 1972; Steele *et al.*, 1974). In order to obtain diagnostic information, sufficiently high count rates and a time resolution of at least 50 milliseconds per frame are necessary (Schad, 1977). Spatial resolution is a recognised limitation of the radionuclide method when compared with angiocardiographic techniques. We, therefore, determined the ratio of the end-systolic to end-diastolic length of the left ventricular circumference (perimeter index); this is a reliable angiocardiographic measurement and there was an acceptable correlation ($r = 0·72$) between measurements of this index made by the two methods. Our studies also confirm that the radionuclide technique provides a means of non-invasive diagnosis of left ventricular dyskinesis. Because of the lesser spatial resolution it is not so sensitive as contrast ventriculography. Nevertheless, 80 per cent of all dyskinetic segments were detected; this technique could thus be very useful for the diagnosis of left ventricular aneurysms in the critically ill patient in the coronary care unit.

In determining ejection fraction the radionuclide method does not suffer from the dependence on ventricular geometry encountered with the angiocardiographic and echocardiographic techniques

(Henning *et al.*, 1975). This independence is a major advantage for quantitative studies. Since blood radioactivity recorded from a correctly delineated left ventricle is proportional to blood volume, the time activity curve corrected for background is a measure of volume change versus time. Therefore, if the time activity curve is recorded from the entire left ventricle, quantification of left ventricular volume changes with time is possible. Contrast angiocardiography commonly tends to give higher values of ejection fraction than the radionuclide method, a difference which can be explained by methodological differences: contrast angiocardiography uses a geometrical model of the left ventricle whereas radionuclide angiocardiography provides a left ventricular volume measurement which is less dependent on the geometry of the ventricle. This difference becomes most obvious in patients with left ventricular aneurysms, where measurements of volume derived from a single plane angiocardiographic projection using a geometrical model must differ from those obtained by the integration of changes in radioactivity within the left ventricular chamber.

On the other hand, several important points have to be considered when ejection fraction is calculated from left ventricular time activity histograms. Firstly, precise fitting of the region of interest to the left ventricular silhouette is critical, especially the proper alignment of the plane of the aortic valve. Secondly, adequate count rates are necessary: we recorded count rates of between 14 000 and 17 000 cps within the entire field of the detector when the bolus passed through the right ventricle. Thirdly, correction for non-cardiac background activity is important: background correction was made by determining the time course of activity in a semicircular region of interest surrounding the apex and the anterior wall of the end-diastolic image. The time activity curve obtained in this way showed a pattern opposite to that of the diastolic and systolic changes of the left ventricular histogram; this was normalised for the size of the left ventricular area and then subtracted from the left ventricular time activity curve. Background correction is a very critical point of the method, since large background areas involving the aorta tend to give results which overestimate ejection fraction, compared with values obtained angiocardiographically. We have found that ejection fraction is significantly underestimated if correction for background is omitted.

There is also evidence from our results that ejection fraction might be a more sensitive indicator of disturbed left ventricular function and thus superior to other haemodynamic measurements which can be made at the bedside (pulmonary artery pressure, left ventricular end-diastolic pressure, cardiac index, etc.) in predicting mortality or identifying those patients who might develop pump failure or cardiogenic shock. Since the extent of akinesis is a reflection of infarct size, it can be considered an important prognostic indicator, and may also serve as an indicator of the effect of interventions aimed at reduction of infarct size.

In conclusion, the combined use of both radioactive tracer techniques, static ^{201}Tl imaging, and dynamic studies with ^{99m}Tc-HSA, provides a non-invasive method for the evaluation and management of patients with coronary artery disease. The technique can be used on an outpatient basis or at the bedside; it facilitates selection of patients for cardiac catheterisation, provides information which can be used as a guide to prognosis, and can be used to assess the effect of therapeutic interventions.

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Plasma adrenaline and noradrenaline concentrations and dopamine-β-hydroxylase activity in myocardial infarction with and without cardiogenic shock

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SUMMARY In patients with myocardial infarction, with or without cardiogenic shock, plasma noradrenaline and adrenaline concentrations are increased. However, plasma noradrenaline concentrations are considerably higher in patients with cardiogenic shock when compared with those with uncomplicated myocardial infarction. Plasma noradrenaline and adrenaline concentrations showed a sustained increase until death in patients with cardiogenic shock whereas those concentrations were back to normal levels by the end of the third day in patients with uncomplicated myocardial infarction. Plasma dopamine-β-hydroxylase activities in both the groups were within normal range and did not show any significant variation throughout the period of study.

It has been proposed that plasma noradrenaline and adrenaline concentrations (Von Euler, 1964) and dopamine-β-hydroxylase (DβH) activities (Axelrod, 1972) may provide information about the function of the sympathetic nervous system and adrenal medulla. Recent technical advances allow these factors to be measured in small volumes of plasma (0·5 ml) and this means that frequent blood sampling can be carried out to monitor dynamic changes in sympathetic nervous system and adrenal medullary function during the course of an illness.

The primary purpose of this study was to determine the changes in plasma noradrenaline and adrenaline concentrations and DβH activities during an illness in which sympathetic nervous activity is traditionally accepted as being increased, that is cardiogenic shock from myocardial infarction. This necessitated a comparison with uncomplicated cases of myocardial infarction and other 'control' groups of patients. Several studies have already been done showing that urinary excretion of catecholamines (Klein *et al.*, 1968; Hayashi *et al.*, 1969; Jewitt *et al.*, 1969; Prakash *et al.*, 1972) and plasma catecholamine concentrations (Gazes *et al.*, 1959; McDonald *et al.*, 1969; Griffiths and Leung, 1971; Januszewicz *et al.*, 1971; Siggers *et al.*, 1971; Lukomsky and Oganov, 1972; Videbaek *et al.*, 1972) are raised in the acute phase of myocardial infarction. A secondary purpose was to see whether there was any relation between plasma noradrenaline and adrenaline concentrations and the severity of the myocardial infarction and its circulatory effects.

Patients and methods

PATIENTS

Patients who were admitted to the coronary care unit with myocardial infarction with or without cardiogenic shock were investigated.

(1) *Patients with cardiogenic shock after myocardial infarction*

The defintition of cardiogenic shock was as follows: systolic blood pressure less than 90 mmHg or 30 mmHg less than the systolic pressure before admission; peripheral cyanosis with cold clammy extremities and oliguria of less than 20 ml/h. Tachycardia and altered level of consciousness were not included because patients in cardiogenic shock often have a slow pulse caused by sinus bradycardia or conduction defects and remain mentally alert. Eleven men and one woman aged 59·2 ± 3·7 years (mean ± SEM) were included in this group.

(2) *Patients with myocardial infarction without cardiogenic shock*

All the patients had a typical history with well-defined onset, electrocardiographic changes diagnostic of acute myocardial infarction, and raised lactic

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dehydrogenase (LDH) (cardiospecific fraction) over 600 IU/ml. Six male and 2 female patients aged 59·10 ± 3·9 years were included in this group.

Previous studies indicated that the occurrence of cardiac arrhythmias in these patients is associated with high plasma catecholamine concentrations (Jewitt *et al.*, 1969; McDonald *et al.*, 1969; Griffiths and Leung, 1971; Siggers *et al.*, 1971). Since the aim of the study was to investigate the relation between plasma adrenaline and noradrenaline concentrations and DβH activities and clinical evidence of shock, cases with more than transient arrhythmias were excluded. Patients who received isoprenaline or noradrenaline were not included as these drugs interfere with the assay for plasma adrenaline and noradrenaline. Patients who received any beta-blocking drugs during the week before admission or after admission were excluded because these drugs may alter plasma catecholamine concentrations (Brecht *et al.*, 1976; Rahn *et al.*, 1976). Venous blood samples, 5 ml, were collected on admission, after 30 minutes of supine rest and then at 4-hourly intervals for the first 12 hours, at 6-hourly intervals for the next 36 hours, and then at 8-hourly intervals for the rest of the period of study.

In all patients the following factors were monitored. Hourly measurement of (i) blood pressure, (ii) pulse rate, (iii) urinary output (in patients with cardiogenic shock indwelling catheters were used); 24-hour monitoring for cardiac arrhythmias; daily chest *x*-ray film, and frequent clinical examination for the detection of pulmonary oedema; daily measurement of LDH (cardiospecific fraction). None of the patients in the 2 groups received any drugs other than the following: diamorphine, oxygen by facial mask, 5 per cent dextrose intravenous drip with or without lignocaine, frusemide intravenously or orally, and either nitrazepam or diazepam.

All the patients with myocardial infarction without complications were transferred to a general ward after 3 to 4 days' stay in the coronary care unit and all eventually went home. Of the 12 patients with cardiogenic shock, 11 died 6 to 48 hours after admission to the coronary care unit.

'CONTROL' GROUP OF PATIENTS

The third and fourth groups of patients consisted of age and sex matched controls.

(3) *Patients admitted for cardiac catheterisation*

Six patients (3 men and 3 women aged 42·0 ± 2·7 years) with congenital heart disease who were normotensive, not in congestive cardiac failure, and not taking any drugs were included in this group. A venous blood sample was collected after 30 minutes of bed rest at the time of admission, at 12, 24, and 48 hours after admission and, finally, before discharge. The cardiac catheterisation was performed 14 to 18 hours after admission and all patients received pethidine 50 to 100 mg intramuscularly before the procedure.

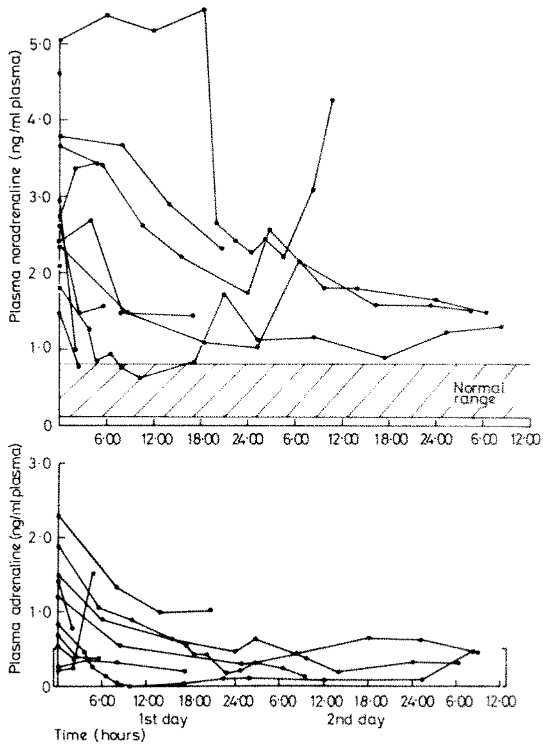

Fig. 1 *Serial estimation of plasma noradrenaline* (above) *and adrenaline* (below) *in cardiogenic shock. For conversion to SI units: adrenaline, 1 ng/ml ≈ 5·458 nmol/l; noradrenaline, 1 ng/ml ≈ 5·9101 nmol/l.*

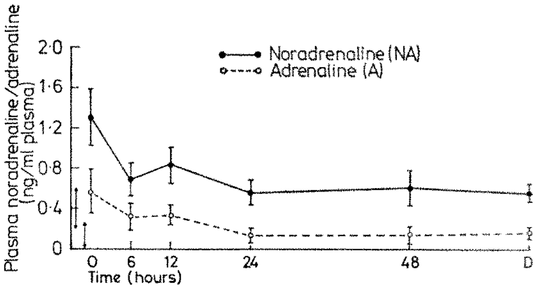

Fig. 2 *Serial estimation of plasma noradrenaline* (above) *and adrenaline* (below) *in myocardial infarction without complication. For conversion to SI units: adrenaline, 1 ng/ml ≈ 5·458 nmol/l; noradrenaline, 1 ng/ml ≈ 5·9101 nmol/l.*

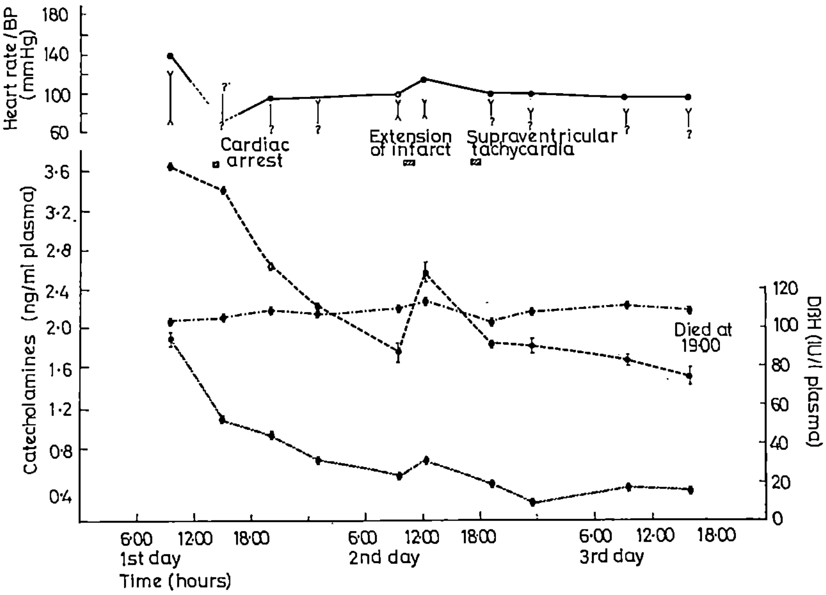

Fig. 3 *Sequential measurement of plasma noradrenaline (-----), adrenaline (-ı-ı-ı-ı-), and dopamine-β-hydroxylase (—·—·—), and blood pressure (Ţ), and heart rate (———) in a patient with cardiogenic shock. For conversion to SI units: adrenaline, 1 ng/ml ≈ 5·458 nmol/l; noradrenaline, 1 ng/ml ≈ 5·9101 nmol/l.*

(4) *Patients admitted with other disease*

Ten patients (5 men and 5 women aged 42·5±5·5 years) admitted with the following acute illnesses were included in this group: (1) lobar pneumonia, (2), (3), and (4) acute appendicitis, (5) systemic lupus erythematosus with fever and impairment of the renal function, (6) urinary tract infection, (7) pleurisy, (8) acute cholecystitis, (9) renal colic, (10) acute pericarditis. Venous blood samples were collected after 30 minutes of bed rest from all these patients within 2 hours of admission and then daily for 5 days by which time their acute symptoms were subsiding. None of these patients was clinically hypovolaemic or hypotensive and none had septicaemia.

Plasma adrenaline and noradrenaline concentrations were measured by a radioenzymatic method (Hörtnagl *et al.*, 1977) while DβH activity was measured by a photometric method (Nagatsu and Udenfriend, 1972). The normal range for plasma LDH activity was 240 to 525 IU/ml. The data, expressed as mean ± SEM, were analysed using Student's unpaired t test (2-tailed).

Results

(1) PLASMA ADRENALINE AND NORADRENALINE CONCENTRATIONS AND DβH ACTIVITIES

(a) *Patients with cardiogenic shock*

These patients were admitted with cardiogenic shock or developed it within 6 hours of admission.

In these patients plasma noradrenaline concentrations at the time of admission, 17·4±1·9 nmol/l (2·94±0·32 ng/ml) (Fig. 1) were greater than the corresponding concentrations for patients with uncomplicated myocardial infarction, 7·7±1·7 nmol/l (1·30±0·28 ng/ml) (Fig. 2) ($P<0·005$),

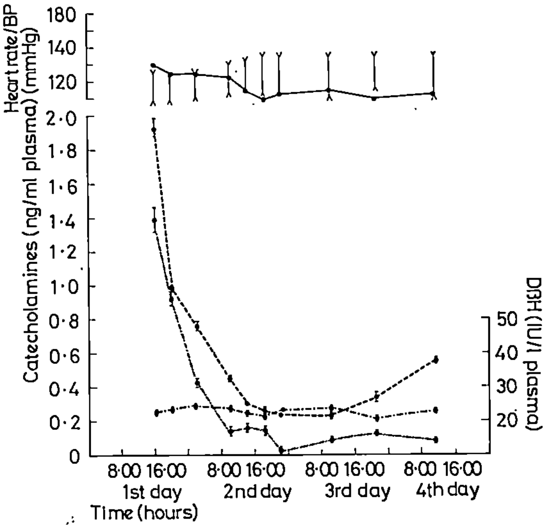

Fig. 4 *Sequential measurement of plasma noradrenaline (-----), adrenaline (-ı-ı-ı-ı-), and dopamine-β-hydroxylase (—·—·—), and blood pressure (Ţ), and heart rate (———) in a patient with uncomplicated myocardial infarction. For conversion to SI units: adrenaline 1 ng/ml ≈ 5·458 nmol/l; noradrenaline, 1 ng/ml ≈ 5·9101 nmol/l.*

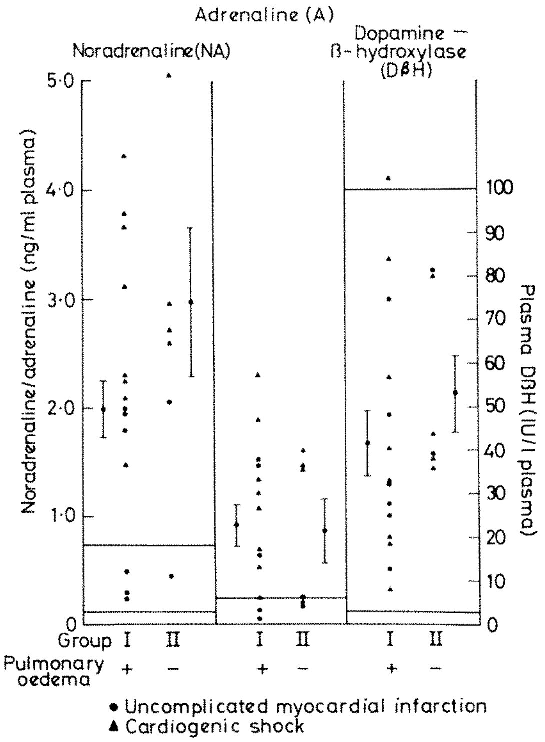

Fig. 5 *Comparison of the admission values of noradrenaline (NA), adrenaline (A), and dopamine-β-hydroxylase (DβH) (mean ± SEM) in patients who had pulmonary oedema on admission with that of patients without it on admission. For conversion to SI units: adrenaline, 1 ng/ml ≈ 5·458 nmol/l. Nonadrenaline 1ng/ml ≈ 5·910 nmol/l.*

patients admitted for catheterisation, 1·7 ± 0·06 nmol/l (0·29 ± 0·02 ng/ml) P < 0·001), and patients with various diseases 2·7 ± 0·4 nmol/l (0·46 ± 0·06 ng/ml) (P < 0·001) (Table 1). Though these increased noradrenaline concentrations declined slightly with time, the concentrations measured 1 to 4 hours before the death of the patients, 11·2 ± 2·1 nmol/l (1·89 ± 0·35 ng/ml) remained higher than the noradrenaline concentrations measured in patients with uncomplicated myocardial infarction when they were admitted to the coronary care unit (P < 0·05).

The plasma adrenaline concentrations in patients with cardiogenic shock at the time of admission were 6·17 ± 1·04 nmol/l (1·13 ± 0·19 ng/ml) (Fig. 1) which were not significantly different from the adrenaline concentrations measured in patients with uncomplicated myocardial infarction, 3·11 ± 1·15 nmol/l (0·57 ± 0·21 ng/ml) (Fig. 2), but were significantly greater than the corresponding values for patients admitted for cardiac catheterisation, 0·76 ± 0·22 nmol/l (0·14 ± 0·04 ng/ml), (P < 0·005), and patients admitted with various disorders, 3·17 ± 0·49 nmol/l (0·58 ± 0·09 ng/ml) (P < 0·05) (Table). Though the plasma adrenaline concentrations declined in patients with cardiogenic shock the concentrations measured 1 to 4 hours before the death of the patient, 2·78 ± 0·76 nmol/l (0·51 ± 0·14 ng/ml) were still considerably above the normal range.

The plasma DβH activities measured in patients with cardiogenic shock on admission (46·7 ± 3·8 IU/l) were not significantly different from the corresponding values in patients with uncomplicated myocardial infarction (42·6 ± 8·6 IU/l) or the 2 'control' groups of patients (Table).

An example of a patient with cardiogenic shock who was investigated is given below (Fig. 3).

Case 1: A 73-year-old man with a past history of ischaemic heart disease was admitted to the coronary care unit with anterior myocardial infarct. On admission he was shocked and had a blood pressure of 90/55 mmHg, with a sinus tachycardia of 136/min, and was in pulmonary oedema with pale cold extremities. Soon after admission the patient arrested and he was resuscitated, but only his systolic blood pressure was recordable. On the second day of his stay in the coronary care unit he had an extension of his myocardial infarct followed by a 10-minute episode of supraventricular tachycardia. The patient died on the third day after admission and necropsy showed a fresh anterolateral infarct.

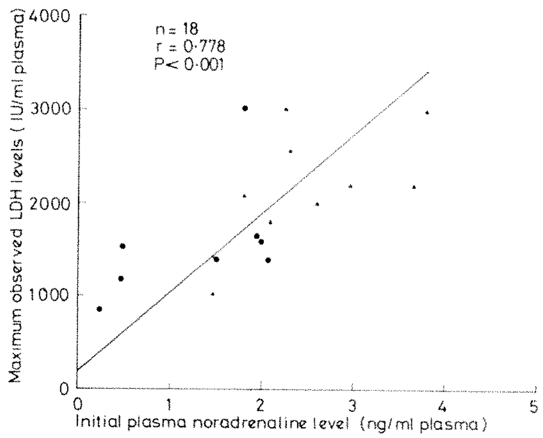

Fig. 6 *Correlation of maximum observed LDH levels (cardiospecific fraction) with plasma noradrenaline levels observed at the time of admission (●—myocardial infarction; ▲ cardiogenic shock). For conversion to SI units: adrenaline, 1 ng/ml ≈ 5·458 nmol/l; noradrenaline, 1 ng/ml ≈ 5·9101 nmol/l.*

(b) *Patients with myocardial infarction without complications*

The plasma noradrenaline concentrations present in patients with uncomplicated myocardial infarction at the time of admission, 7·7 ± 1·7 nmol/l (1·30 ± 0·28 ng/ml) (Fig. 2), were significantly greater than the corresponding values for the patients admitted for cardiac catheterisation, 1·7 ± 0·1 nmol/l (0·29 ± 0·02 ng/ml), $(P < 0·01)$ and the values for patients admitted with various other diseases, 2·7 ± 0·4 nmol/l (0·46 ± 0·06 ng/ml), $(P < 0·02)$ (Table). The increased noradrenaline concentrations gradually declined after admission and within 48 to 72 hours after admission to the unit the concentrations were similar to normal values in healthy subjects.

The plasma adrenaline concentrations in patients with uncomplicated myocardial infarction were increased at the time of admission, 3·11 ± 1·15 nmol/l (0·57 ± 0·21 ng/ml) (Fig. 2). They were not significantly different from the corresponding concentrations of adrenaline measured in patients with various other diseases, 3·17 ± 0·49 nmol/l (0·58 ± 0·09 ng/ml) or from those measured in patients admitted for cardiac catheterisation, 0·76 ± 0·23 nmol/l (0·14 ± 0·04 ng/ml) (Table). The increased plasma adrenaline concentrations in patients with uncomplicated myocardial infarction returned to normal within 24 hours of admission.

An example of a patient with uncomplicated myocardial infarction who was investigated is given below.

Case 2 (Fig. 4): A 39-year-old man with a past history of myocardial infarction was admitted to the coronary care unit with an acute anteroinferior myocardial infarct. On admission he had a blood pressure of 105/70 mmHg and a pulse rate of 80/min. He was pale and sweating profusely but did not have pulmonary oedema. His hospital course was uncomplicated and he was discharged on the 11th day after admission.

(c) *Patients admitted for cardiac catheterisation*

The plasma noradrenaline and adrenaline concentrations and DβH activities measured in these patients are given in the Table. Plasma adrenaline and noradrenaline concentrations and DβH acjivities in this group of patients were within normal range. There were no significant changes in any of these measurements before and immediately after catheterisation.

(d) *Patients admitted with 'various diseases'*

The plasma noradrenaline and adrenaline concentrations and DβH activities measured in these patients are given in the Table. Though in these patients the plasma noradrenaline concentrations and DβH activities were not increased at the time of admission the plasma adrenaline concentrations *were* increased. The increased plasma adrenaline concentrations returned to normal with 2 to 3 days of admission to hospital.

(2) CORRELATION BETWEEN PRESENCE OR ABSENCE OF PULMONARY OEDEMA AND PLASMA NORADRENALINE AND ADRENALINE CONCENTRATIONS AND DβH ACTIVITIES AT TIME OF ADMISSION

All the patients with myocardial infarction, whether in cardiogenic shock or not, were divided into 2 groups, those who had pulmonary oedema detectable clinically and radiologically at the time

Table *Plasma adrenaline (A), noradrenaline (NA), and dopamine-β-hydroxylase (DβH) concentrations in 'control' patients (mean ± SEM)*

		On admission	*12 hours*	*24 hours*	*48 hours*	*At the time of discharge*
Cardiac catheterisation group	A (ng/ml)*	0·14 ± 0·04	0·17 ± 0·05	0·18 ± 0·04	0·16 ± 0·05	0·15 ± 0·03
	NA (ng/ml)†	0·29 ± 0·02	0·28 ± 0·02	0·29 ± 0·03	0·30 ± 0·03	0·30 ± 0·02
	DβH (IU/l)	39·18 ± 2·34	39·27 ± 2·15	39·52 ± 2·08	37·83 ± 2·1	38·97 ± 2·14
		On admission	*24 hours*	*48 hours*	*72 hours*	*96 hours*
Various disease group	A (ng/ml)	0·58 ± 0·09	0·55 ± 0·06	0·33 ± 0·04	0·16 ± 0·06	0·17 ± 0·05
	NA (ng/ml)	0·46 ± 0·06	0·45 ± 0·05	0·48 ± 0·03	0·42 ± 0·03	0·40 ± 0·06
	DβH (IU/l)	50·26 ± 2·86	52·71 ± 2·45	50·56 ± 2·32	48·64 ± 2·36	47·46 ± 2·38

The normal range for this laboratory (Hörtnagl *et al.*, 1977)

$$\left.\begin{array}{ll} \text{A} & = < 0·02\text{–}0·26\ \text{ng/ml} \\ \text{NA} & = 0·23\text{–}0·72\ \text{ng/ml} \\ \text{D}\beta\text{H} & = 2·2\text{–}88·6\ \text{IU/l} \end{array}\right\} n = 16$$

* For conversion to SI units 1 ng/ml ≈ 5·458 nmol/l.

† For conversion to SI units 1 ng/ml ≈ 5·9101 nmol/l.

of admission and those who did not. The plasma noradrenaline and adrenaline concentrations and DβH activities measured in those 2 groups of patients are given in Fig. 5 and are not significantly different.

(3) RELATION BETWEEN PEAK CARDIOSPECIFIC LDH CONCENTRATIONS AND PLASMA NORADRENALINE AND ADRENALINE CONCENTRATIONS AND DβH ACTIVITIES MEASURED AT TIME OF ADMISSION

The maximum cardiospecific LDH concentration (found at 3 to 5 days after the infarct) measured in patients with myocardial infarction (including those with cardiogenic shock) was plotted against the plasma noradrenaline concentrations present at the time of admission (Fig. 6). There was a significant correlation between the 2 variables ($r = 0.778$; $P < 0.001$). However, there was no correlation between either plasma adrenaline concentrations or DβH activity and the maximum cardiospecific LDH concentrations.

Discussion

The present study differs from other studies in this field in that plasma adrenaline and noradrenaline concentrations were measured at frequent intervals by a sensitive radioenzymatic method at the same time as DβH activity estimation.

When patients who were not acutely ill were admitted to hospital plasma noradrenaline and adrenaline concentrations and DβH activities did not change significantly (cardiac catheterisation group). This supports the finding of McDonald *et al.* (1969) that the stress of admission to hospital and of investigation does not alter plasma catecholamine concentrations.

Plasma noradrenaline concentrations are raised in patients with myocardial infarction and are considerably raised in patients with cardiogenic shock. Plasma noradrenaline concentrations in both the 'control' groups were within the normal range.

There was a significant correlation between plasma noradrenaline concentrations and maximum observed cardiospecific LDH activities which is a crude index of infarct size (Killen and Tinsley, 1966). A similar relation between urinary excretion of noradrenaline and cardiospecific LDH activities has been noted. It is possible that the bigger the size of the myocardial infarct the greater is the extent of sympathetic stimulation, which may explain the correlation between plasma noradrenaline concentration and LDH activity.

McDonald *et al.* (1969) found a significant correlation between the presence of pulmonary oedema and increased plasma catecholamine concentrations. We did not find any such correlation, confirming the findings of Siggers *et al.* (1971) who found no correlation between peak values of plasma adrenaline or noradrenaline concentrations and presence of pulmonary oedema. The absence of pulmonary oedema in our patients, particularly those with cardiogenic shock, possibly could be the result of infarction involving the right as well as the left ventricle or could simply be because the number of patients studied was small.

When patients with uncomplicated myocardial infarction or with 'various diseases' were admitted their plasma adrenaline concentrations were significantly higher than those of patients admitted for catheter studies and returned to normal within 3 to 4 days. In contrast, in patients with cardiogenic shock there was an even greater increase in plasma adrenaline concentrations which remained raised until they died. This suggests that in patients with acute illness there is increased adrenal medullary function which rapidly returns towards normal as the patient recovers, while in those with cardiogenic shock the activity of the adrenal medulla remains high.

There was no significant difference in plasma DβH activities among the 4 groups and sequential changes in all the groups were not significantly different. Gutteberg *et al.* (1976) reported that DβH activities found during the first 2 days after myocardial infarction were significantly different from the DβH activities present 10 days after infarction. We did not, however, follow our patients up to 10 days. It is evident from our study that measurement of plasma DβH activities is not a useful index of sympathetic nervous system function when compared with determinations of plasma noradrenaline concentrations.

Although rises in plasma noradrenaline and adrenaline might be accounted for by several processes, that is increased release and decreased removal by re-uptake and metabolism, it seems very likely, taking into account the clinical picture, that sympathetic nervous system and adrenal medullary function are increased in myocardial infarction and if cardiogenic shock ensues the increased activity is even more obvious.

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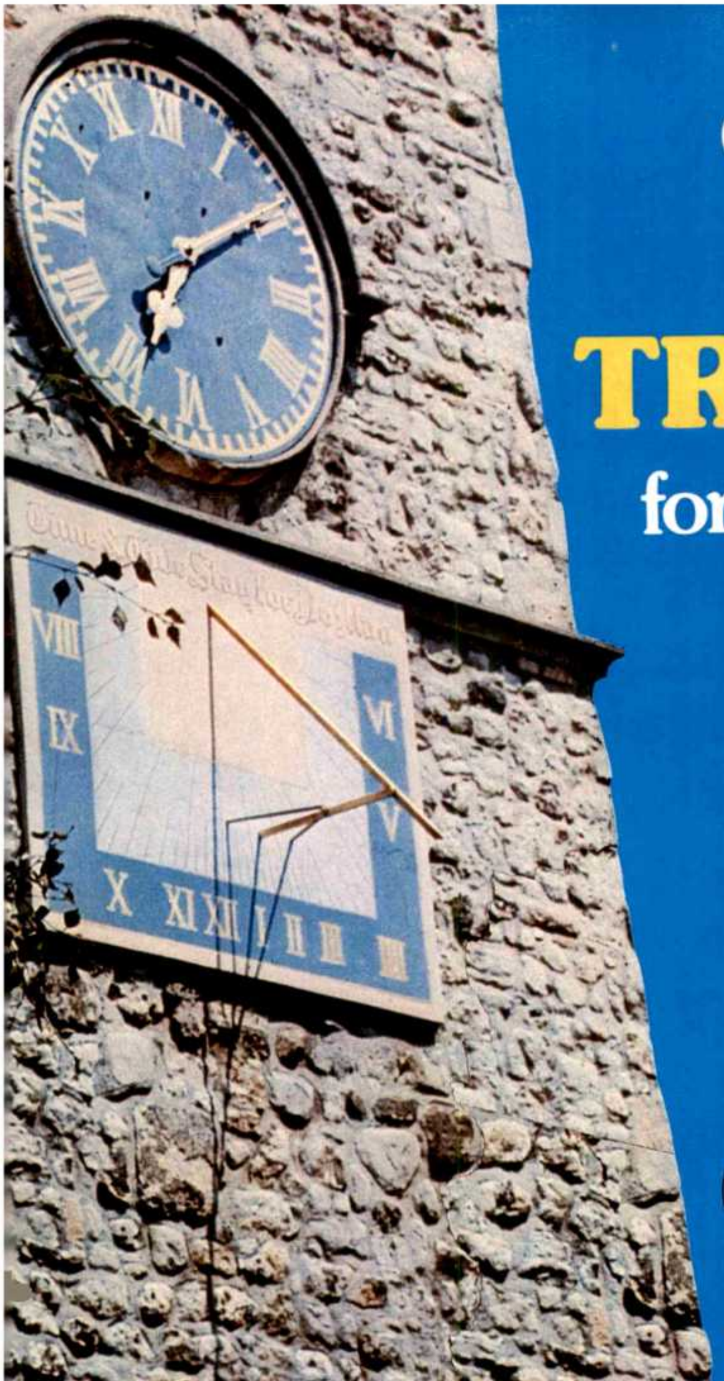

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Am. J. Cardiol. (1977) **39,** 91, Bussmann WF et al : Orally administered isosorbide dinitrate in patients with and without left ventricular failure due to acute myocardial infarction.

Circulation (1977) **55,** 381, Danahy DT et al : Sustained hemodynamics and antianginal effect of high dose oral isosorbide dinitrate.

Am. J. Cardiol. (1977) **39,** 84, Williams DO et al : Hemodynamic assessment of oral peripheral vasodilator therapy in congestive heart failure : prolonged effect of isosorbide dinitrate.

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British Heart Journal, 1979, **42**, 221-223

Myxoma of the mitral valve

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SUMMARY A case of myxoma of the mitral valve is reported. The clinical features were indistinguishable from left atrial myxoma with prolapse through the mitral valve. Because of the known tendency for these tumours to recur it was treated by wide excision which necessitated replacement of the mitral valve.

Myxomas, though rare, are the most common intracavitary cardiac tumours and account for over half of all primary cardiac neoplasms (Heath, 1968). The great majority occur in the left and right atria, usually arising from the vicinity of the fossa ovalis. Myxomas may rarely be found in other regions of the heart such as the right (Gottsegen *et al.*, 1963) and left (Kay *et al.*, 1959) ventricles and Prichard's extensive review of the subject in 1951 included reference to a primary myxoma of the mitral valve.

The purpose of this report is to document an unusual case of myxoma of the mitral valve and describe how surgical management was influenced by consideration of the malignant potential of these tumours.

Case report

A 33-year-old housewife presented in 1975 with an 11-year history of intermittent attacks of shortness of breath. Initially these were of abrupt onset and often unrelated to effort. In 1968 a clinical diagnosis of mixed mitral valve disease had been made and this was judged to be of mild degree on the basis of a good performance on the bicycle ergometer and low pressures at right heart catheterisation. The episodic nature of her symptoms was ascribed to paroxysmal tachycardia. In 1973 she developed atrial fibrillation and there was pronounced deterioration in her exercise tolerance.

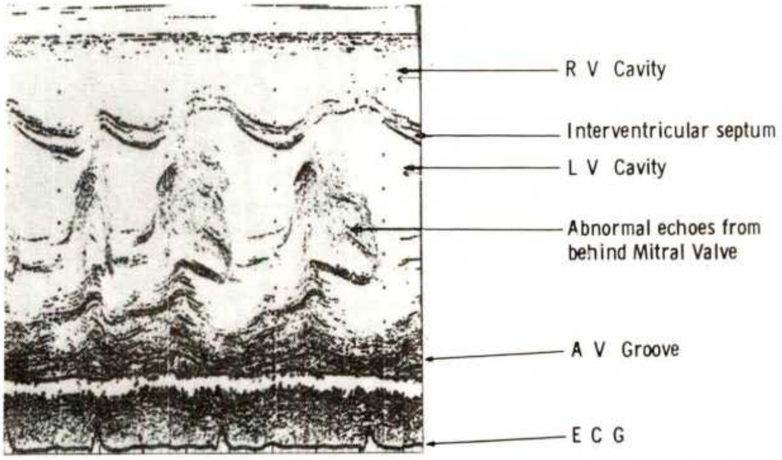

Fig. 1 *Preoperative echocardiogram illustrating abnormal dense echoes behind anterior cusp of mitral valve.*

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On examination in July 1975 she was comfortable at rest but breathless on mild exertion. The pulse was 96 per minute and irregular and the blood pressure 120/70 mmHg. The jugular venous pressure was not raised. The apex beat was palpable in the sixth left intercostal space in the mid-clavicular line. There was a left parasternal heave and a diastolic thrill over the apex. On auscultation there was an extremely loud first sound with a late systolic murmer and a rumbling mid-diastolic murmur. The electrocardiogram confirmed the presence of atrial fibrillation and the chest radiograph showed cardiomegaly, with a cardiothoracic ratio of 14·5: 27. At cardiac catheterisation the mean capillary wedge pressure was 30 mmHg. The pulmonary arterial pressure was 60/30 mmHg at rest, rising to 100/50 mmHg on exercise. The left ventriculogram showed moderate mitral reflux into a large left atrium. No filling defect was noticed in the left ventricle or left atrium and there was no calcification in the region of the mitral valve. An echocardiogram of the mitral valve (Fig. 1) showed a normal, mobile anterior cusp with multiple dense echoes posterior to it suggestive of a tumour mass in this region.

At operation on 6 October 1975 the external appearance of the heart was consistent with chronic mitral valve disease with moderate enlargement of the cardiac chambers, a dilated pulmonary artery, and a small aorta. On cardiopulmonary bypass the left atrial cavity was explored and a large myxoma 3·5 × 4·5 × 1·5 cm (Fig. 2) was found arising from a pedicle attached to the anterior cusp of the mitral valve close to the lateral commissure. The tumour was soft and gelatinous with a frond-like structure and was pinkish-yellow in colour. The mitral annulus was dilated but the remainder of the mitral valve and the subvalvar mechanism appeared normal. The right atrium was opened and both surfaces of the atrial septum were inspected. No other myxomas were seen. The tumour was excised with a surrounding cuff of the anterior leaflet of the mitral valve. The resulting defect was too large for a direct repair, so the valve was excised and replaced with a Björk-Shiley prosthesis. Before insertion of the prosthesis, the left atrial and ventricular cavities were carefully flushed out with cold Hartman's solution to remove any fragments of tumour that may have been dislodged during excision. The patient's recovery was satisfactory and she was discharged from hospital 11 days later. Histological examination of the tumour confirmed it to be a myxoma. There was some increase in the normal non-compact myxomatous connective tissue lamina of the mitral valve cusps and a small group of myxoma cells was found in the endocardium of the posterior papillary muscle. Two years later the patient was asymptomatic. She was in sinus rhythm and her heart size was within normal limits, with a cardiothoracic ratio of 12·5: 27.

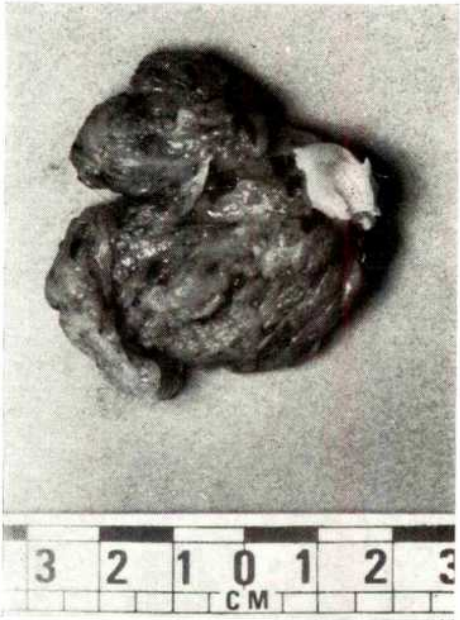

Fig. 1 *Specimen of excised myxoma of the mitral valve.*

Discussion

Intracardiac myxomas are believed to arise from remnants of myxoid tissue of embryonic myocardium. The frequent persistence of such tissue in the region of the fossa ovalis helps to explain the peculiar localisation of these tumours (Yater, 1931).

Atrial myxomas usually present with embolism, obstruction, or constitutional illness (Goodwin, 1963). The obstructive symptoms and clinical presentation of myxoma of the mitral valve are indistinguishable from that of one which arises on the atrial septum and prolapses through the mitral valve. The presence of a filling defect is usually apparent at angiocardiography, but this is sometimes missed and the diagnosis can usually be confirmed by echocardiography (Popp and Harrison, 1969).

Until relatively recently the accepted surgical management for intracardiac myxomas was simple excision of the tumour (Firor *et al.*, 1966). However, since Gerbode and colleagues (1967) reported the first case of recurrent left atrial myxoma, there have been several reports of tumour recurrence, both at and remote from the site of excision (Bahl *et al.*, 1969; Hattler *et al.*, 1970; Walton *et al.*, 1972; Jugdutt *et al.*, 1975). The cause of recurrence is not clear and has been attributed to local implantation of cells by the primary tumour (Kabbani and Cooley, 1973) and the systemic embolisation of myxoma cells (Read *et al.*, 1974). Several reports have drawn attention to an unusually rapid growth rate of the recurrent tumour, and Walton and colleagues (1972) described an interesting case in which recurrence occurred within 22 months at the site of removal of the previous tumour, despite excision of a surrounding cuff of atrial septum. Careful histological examination of the piece of septum removed at the initial operation failed to show any tumour cells and they suggested that recurrence might have been from growth from 'pre-tumour' cells in this area. The malignant potential of atrial myxoma was stressed in a review of recurrent tumours by Read and colleagues (1974), and they described one patient who developed metastatic myxomas in the sternum and pelvis 6 years after excision of an atrial myxoma. The metastatic tumours appeared histologically more cellular, pleomorphic, and malignant, but were otherwise similar to the original atrial tumour. These authors also reported the first patient on record to develop a recurrent myxoma on his mitral valve, for which valve replacement was required.

Because of the prevailing uncertainty with regard to the prognosis of these tumours, we agree with Kabbani and Cooley (1973) that a radical approach is indicated at the primary operation. In addition, precautions should be taken to prevent tumour embolism during operation and both atria should always be explored to exclude the presence of multicentric tumours. Application of these principles in the case presented led to excision of the mitral valve, whereas a conservative operation might otherwise have been performed. The subsequent histological demonstration of a small group of myxoma cells in the endocardium of the posterior papillary muscle was an unexpected finding and could represent either a multicentric focus or implantation of cells by the primary tumour.

We are grateful to Dr P. G. I. Stovin for interpretation of the histological findings.

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Constrictive endocarditis
Report of a case with successful surgery

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SUMMARY An 18-year-old white youth presented with severe right heart failure and was found to have an obliterated and funnel-shaped right ventricle, massive tricuspid regurgitation, and mitral regurgitation. The haemodynamic findings were those of cardiomyopathy with obliteration on the right side. He underwent surgery consisting of decortication and peeling off of a thickened right ventricular endocardium, tricuspid valve replacement, and mitral valve repair. After surgery there was pronounced haemodynamic as well as clinical improvement. The pathological picture was that of constrictive endocarditis. We recommend this method of treatment for patients with obliterative cardiomyopathy on either side of the heart.

A variety of cardiac disorders characterised by thickening of the endocardium and involvement of myocardium have been described. Despite the relatively unique modes for their clinical presentation, because of minor differences in pathology they have been classified differently, namely: endocardial fibroelastosis (Van Buchem *et al.*, 1959; Moller *et al.*, 1964; Sellers *et al.*, 1964), endomyocardial fibrosis (Shillingford and Somers, 1961; Moller *et al.*, 1964; Somers *et al.*, 1968a, b; Falase *et al.*, 1976), Loeffler's eosinophilic endocarditis (Brockington and Olsen, 1973; Bell *et al.*, 1976).

The purpose of this paper is to describe a patient with clinical and pathological findings characteristic of constrictive endocarditis, who underwent successful surgery of the lesion. The pre- and postoperative haemodynamic data are presented in detail.

Case report

An 18-year-old white youth was admitted in May 1976 with palpitation, dyspnoea on exertion, chest pain, dizziness, oedema, and swelling of the abdomen.

He had been in fairly good health until 6 years before admission when he developed palpitation and dyspnoea on exertion. During the ensuing 6 years he became progressively incapacitated, developing chest pain, oedema, and ascites. The past and family history were essentially unremarkable, he gave no history of rheumatic fever and no other member of the family had a similar illness.

On physical examination he looked ill and pale, but was well developed, weighing 66 kg; heart rate was 76 to 84/min, and irregular, respiration 24/min, and blood pressure was 115/70 mmHg. The peripheral pulses were of good quality. The jugular veins were distended in the sitting position with equal a and v waves. The apical impulse was hyperactive and first and second heart sounds seemed normal. A grade 3-4/6 systolic murmur was heard at the apex with radiation to the left sternal border. The lungs were clear. The liver was palpable 4 to 5 cm below the right costal margin. Ascites was present. All laboratory investigations were within normal limits and no abnormal eosinophilia was noted. The patient underwent a right and left heart catheterisation, with findings characteristic of restrictive endocardial fibrosis (Fig. 1a).

Cineangiography showed that the left ventricle was large and that it contracted poorly; there was severe mitral regurgitation. The right ventricle was almost obliterated, being small and funnel-shaped, with no trabeculation and poor contraction (Fig. 2a); there was massive tricuspid regurgitation. The right atrium was dilated. Despite vigorous medical treatment the clinical course deteriorated, and he agreed to undergo surgery. During operation a huge right atrium and a small right ventricle were seen. The right ventricular endocardium was

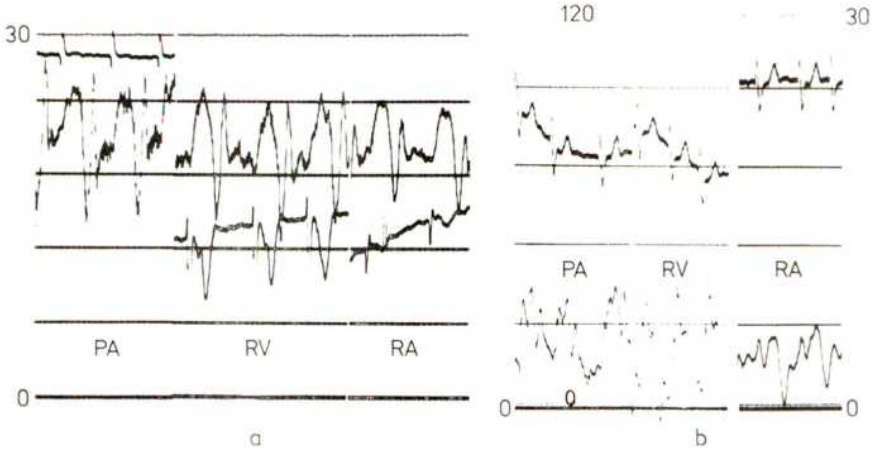

Fig. 1 (*a*) *Right atrial, right ventricular, and pulmonary arterial pressures with intracardiac electrocardiogram before operation showing diastolic plateau and early diastolic dip. Note similar pressure contours in all the chambers and vessels. (Pressure standards 30 mmHg.)* (*b*) *Normal right atrial, right ventricular, and pulmonary arterial pressures after operation.*

extremely thickened and glossy and there were firm adhesions between the right ventricular endocardium, the myocardial fibrotic tissue, and the tricuspid valve. The thickened right ventricular endocardium was extensively peeled off together with the deformed tricuspid leaflets. A number 29

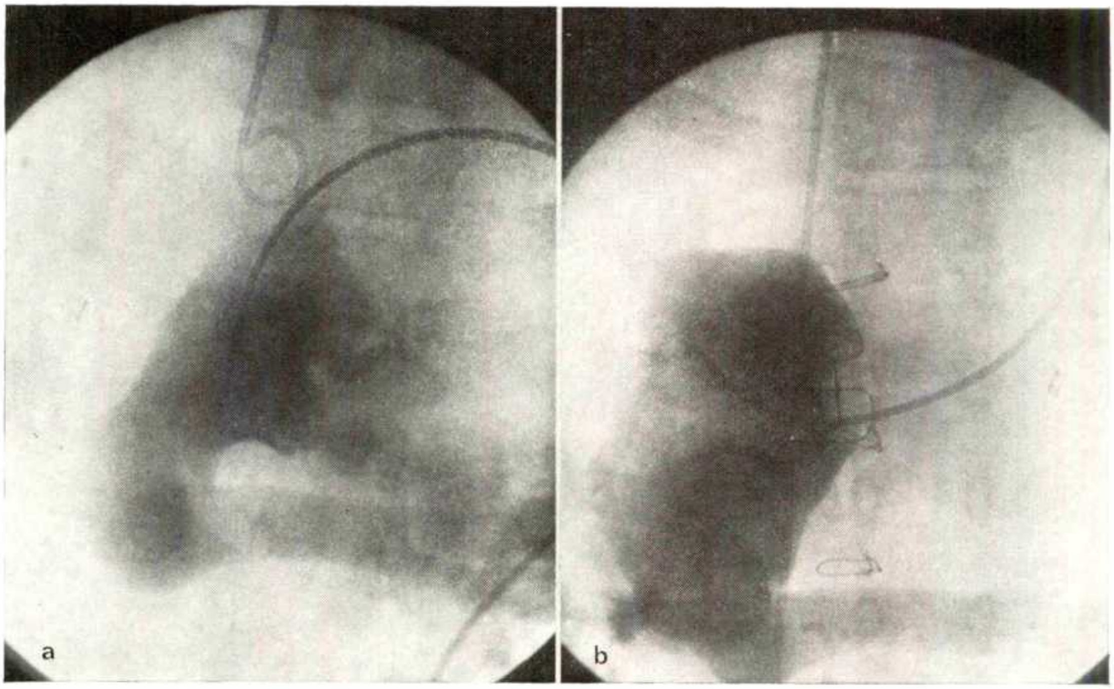

Fig. 2 (*a*) *Frame of cineangiocardiogram obtained from the right ventricle showing a smooth-walled small ventricular chamber with massive tricuspid regurgitation.* (*b*) *Frame of cineangiocardiogram obtained from the right ventricle. Note enlarged right ventricular cavity and absence of tricuspid regurgitation.*

Carpentier valve was inserted in the tricuspid position. The mitral valve was repaired.

The postoperative course was uneventful and the patient had no audible murmur. The congestive heart failure receded and the patient's general condition improved significantly. Chest *x*-ray film showed a conspicuous reduction in heart size. Repeat cardiac catheterisation 6 weeks after operation showed that intracardiac pressures had returned to normal (Fig. 1b), and a right ventricular cineangiogram showed a normal sized chamber with good contraction and no tricuspid regurgitation (Fig. 2b). A left ventricular cineangiogram showed no mitral regurgitation. The patient was maintained on digitalis and at present is leading a fairly normal life.

The endocardial specimen removed during operation consisted of several thick membranous rigid sheets of endocardium with thickness varying from 1·5 to 3 mm. The inner surface of the endocardium was glistening and no mural thrombi were noted.

The parietal surface of the endocardium was partially covered by ragged pieces of myocardial tissue. The dense white endocardial fibrous tissue anchored the papillary muscle and enmeshed the roots of the chordae tendineae. Microscopical sections (Fig. 3) of various parts of the specimen showed distinct thickening of the endocardium with collagen. With Verhoeff van Gieson elastic stain the appearances were unlike those in endocardial fibroelastosis and sections showed irregular masses of broken elastic fibres instead of proliferating tissue. The thickened areas showed destruction of the original endocardium and adjacent superficial myocardium with replacement by vascular fibrous tissue. There were foci of sparse perivascular lymphocytic cell infiltration in the deeper layer of the endocardium.

The pathological diagnosis was constrictive endocardial sclerosis.

Comment

The clinical picture of patients with endocardial fibrosis is similar to that in endomyocardial fibrosis or Loeffler's endocarditis (Shillingford and Somers, 1961; Somers *et al.*, 1968a, b; Brockington and Olsen, 1973; Bell *et al.*, 1976) and classification is principally based on the pathological findings.

Our patient presented with clinical findings of right heart failure and the haemodynamic studies showed the characteristic findings described for endocardial fibrosis of the right ventricle with

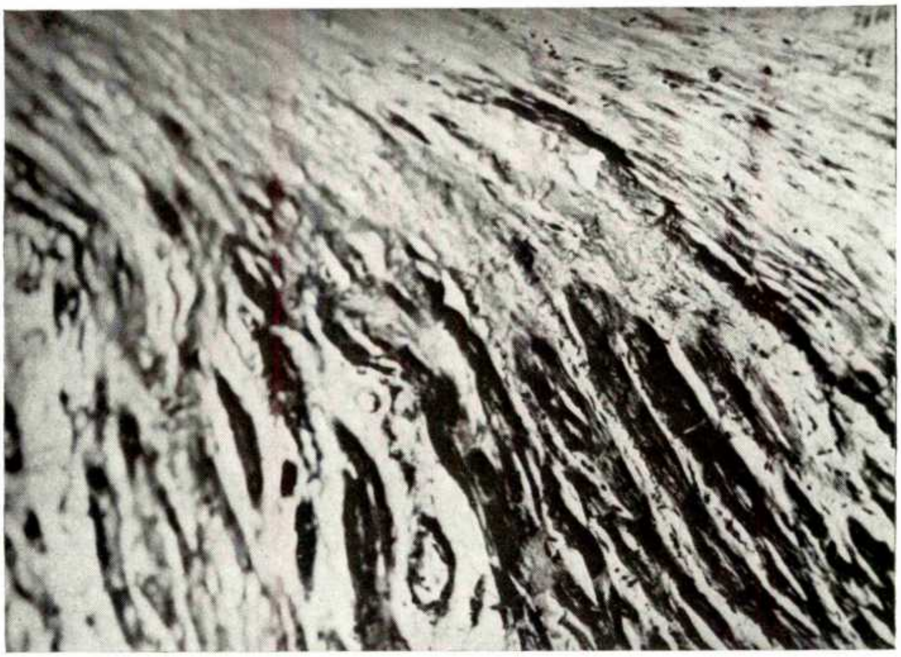

Fig. 3 *Microscopical section of the resected tissue, showing extension of fibrous tissue fascicles from the thickened endocardial layer in between the subendocardial muscle bundles. (Masson's trichrome. × 100.)*

tricuspid regurgitation (Shillingford and Somers, 1961; Somers *et al.*, 1968a, b). The right ventricular angiocardiogram which demonstrated a funnel-shaped and constricted right ventricle led us to diagnose endomyocardial fibrosis as described previously (Somers *et al.*, 1968). The reduced compliance of the right ventricle in our patient resulted in high end-diastolic pressure in this chamber and an increase in right atrial pressure. In the absence of left ventricular endocardial fibrosis, the pulmonary arterial pressure is reported to be normal (Somers *et al.*, 1968).

Although in our case the left ventricular involvement was not as extensive as the right ventricular lesion, poor contraction of the left ventricle was present. Nevertheless during operation no fibrosis was found in the left ventricular endocardium. The overall haemodynamic picture in this case is compatible with generalised myocardial disease with predominant right ventricular involvement.

The pathological findings were interpreted as constrictive endocarditis. It seems that the above entity is a variation of endomyocardial fibrosis. The latter lesion is often described in Africans (Shillingford and Somers, 1961; Somers *et al.*, 1968 a, b), but to our knowledge no cases have been observed in this area. Though Loeffler's endocarditis presents with similar findings (Friedberg, 1966; Brockington and Olsen, 1973; Bell *et al.*, 1976), the reported cases have pronounced eosinophilia during phases of the disease, which was not seen in our case. The pathological findings have differed from those classically described for endocardial fibroelastosis (Van Buchem *et al.*, 1959; Moller *et al.*, 1964; Sellers *et al.*, 1964). In a recent review of endomyocardial fibrosis it was described as a distinct entity different from Loeffler's endocarditis (Patel *et al.*, 1977). Use of the term restrictive cardiomyopathy for the spectrum of the disease has been recently recommended (Chew *et al.*, 1977).

The aetiology of the disease in our case as in most of the published cases remains unknown.

An important point of emphasis in this case is the successful surgery. In an extensive review on the treatment of cardiomyopathies (Goodwin, 1973), the results in obliterative cardiomyopathies were cited as unsatisfactory. Our success with decortication and peeling of the right ventricular endocardium as described by Dubost *et al.* (1976) and Cachera *et al.* (1976) sheds hope on the management of such patients. Dubost's recent article (Dubost *et al.*, 1976) reporting the results of this operation on 5 cases is further support that this method can successfully palliate patients. Clinically our case showed dramatic improvement with resolution of hepatomegaly and ascites. The heart size was reduced and the patient's functional classification improved significantly.

Haemodynamic studies after operation showed distinct improvement and nearly normal intracardiac pressures; angiocardiograms have shown reduction of obliteration and improved ventricular function.

Although the long-term results and future course of the patient are unknown, in view of the extremely poor results of pure medical management in such patients we recommend the above-mentioned method of operation for all patients whose course is one of deterioration with right or left sided obliterative cardiomyopathy. These efforts may perhaps give hope in the management of a potentially incurable heart disease.

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Lone aortic regurgitation, sacroiliitis, and HLA B27
Case history and frequency of association

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SUMMARY An account of aortic regurgitation complicating ankylosing spondylitis is given. Twenty patients with lone aortic regurgitation and without overt spondylitis were examined clinically and radiologically and tissue typed. No evidence of sacroiliitis could be found in any patient. HLA B27 was absent from this group, and no significant disturbance in antigen frequency was noted.

The allele HLA B27 is strongly associated not only with ankylosing spondylitis but also with its *formes frustes,* acute iritis and sacroiliitis in isolation, and with Reiter's syndrome. Aortic regurgitation has been reported in association with ankylosing spondylitis in 2 per cent of cases and characteristically occurs with peripheral joint involvement. Ankylosing spondylitis can present as an acute polyarthritis and fever, particularly in younger patients when it used to be mistaken for rheumatic fever. In this paper we describe such a case and give the results of a pilot study on a possible association between lone aortic regurgitation, sacroiliitis, and histocompatibility antigens.

Case report

A 46-year-old instrument mechanic, who had a history of repeated episodes of arthritis from the age of 13 with back pain since the age of 19, had a diagnosis of aortic regurgitation confirmed at the age of 21 years, though a murmur had first been noted at the age of 15. He was able to lead an active life until 2 years before admission when he became troubled with dyspnoea.

Physical examination disclosed a thin man with an obvious kyphosis and a rigid back. He was in sinus rhythm, with a collapsing pulse; the blood pressure was 190/80 mmHg. There was a systolic murmur at the aortic area and a long early diastolic murmur at the left sternal edge.

The chest *x*-ray film showed severe cardiac enlargement with a dilated aortic root. The sacroiliac joints were fused and the lumbar spine had classic changes of ankylosing spondylitis.

The electrocardiogram showed left ventricular hypertrophy grade III. The echocardiogram showed an enlarged left ventricle with diastolic fluttering of the anterior mitral cusp. Cardiac catheterisation disclosed no evidence of aortic stenosis and no end-diastolic gradient across the mitral valve. Angiography showed severe aortic regurgitation, a tricuspid aortic valve and patent coronary arteries.

At operation the left ventricle was grossly enlarged and hypertrophied and the left atrium was of normal size. The aortic valve was tricuspid with fibrosis extending from the base of the cusp, there was no evidence of calcification or commissure fusion, and there was no evidence of aortic root disease. A satisfactory aortic valve replacement with a Hancock prosthesis was performed.

PILOT STUDY

To examine the possibility that lone aortic regurgitation without overt spondylitis may occur with HLA B27, 20 patients, 12 men and 8 women, were studied. All these patients had lone aortic regurgitation but no past history suggestive of rheumatic fever. Patients were questioned for a history of backache and examined for evidence of spondylitis; *x*-ray films of the lumbar spine and sacroiliac joints were taken and they were tissue typed. Though there was often a history of backache there was no limitation of spinal movement. In none was there radiological evidence of sacroiliitis though degenerative changes were common.

TISSUE TYPING

The technique for tissue typing was as follows.

Peripheral lymphocytes were separated on a Ficoll-sodium metrizoate density gradient, and typed on glass plates employing a two-stage, two-

Table *HLA antigen frequencies in lone aortic regurgitation*

Antigen	*Per cent*	*Antigen*	*(n=20) Per cent*
A1	35	B5	—
A2	65	B7	15
A3	15	B8	30
A9	10	B12	40
AW23	5	B13	—
AW24	5	B14	15
A10	—	B15	20
A25	5	BW16	5
A26	—	B17	15
A11	10	B18	15
AW19	—	BW21	—
AW30	—	BW22	—
AW31/33	5	B27	—
AW32	5	BW35	5
A28	10	BW37	5
A29	15	B40	15
		BW41	—
Blank + 1AG	15	Blank + 1AG	20

colour fluorochromatic microcytotoxicity technique based on the procedure of Bodmer *et al.* (1967).

A panel of 98 HLA antisera, kindly supplied by the National Tissue Typing Reference Laboratory, Bristol, was used to define a total of 16 A-locus and 17 B-locus specificities. Five potent, well-characterised antisera to B27 were included.

The distribution of phenotypes found in the patient group is listed in the Table. HLA B27 was found to be absent from this group. There was no evidence of disturbance in antigen frequency, and analysis using a control group of 417 healthy random Bristol blood donors (C. Entwhistle, personal communication) confirmed that there was no significant deviation.

Discussion

With the decline of rheumatic fever, aortic regurgitation now represents a more heterogeneous group but the association with ankylosing spondylitis is not frequent. Moreover, death from aortic regurgitation complicating this condition is rare, for though deaths from all circulatory diseases were in excess in men suffering from ankylosing spondylitis the difference from the expected was of only borderline significance statistically (Radford *et al.*, 1977).

Various studies report the incidence of HLA B27 in ankylosing spondylitis as greater than 88 per cent (Whitfield, 1976). Of these patients 2 per cent will develop aortic regurgitation which is far in excess of that expected. This implies a relation between HLA B27 and aortic regurgitation in these cases. HLA B27 is associated not only with ankylosing spondylitis but also with acute anterior uveitis alone. That this triad is even more closely linked has been shown by the demonstration of abnormal radioisotope scans of the sacroiliac joint in 19 of 30 patients with acute anterior uveitis, none of whom had clinical or radiographic evidence of sacroiliitis. Of these 19, 11 carried HLA B27 (Russell *et al.*, 1976). The association between this allele and acute anterior uveitis in the absence of clinical or radiographic evidence of sacroiliitis leads to speculation on an association between HLA B27 and aortic regurgitation occurring without overt sacroiliitis or spondylitis. Though the numbers are small, it is evident from our figures that there can be no strong correlation.

Whitfield (1976) reports that cardiac manifestations of ankylosing spondylitis tend to be seen in the most severe forms of the disease as judged by degree of disability and peripheral joint involvement. This could explain the negative correlation of our findings. The association of aortic regurgitation with more severe ankylosing spondylitis implies that the aortic valve and root are less susceptible than the articular structures to the disease process, and that the development of aortic regurgitation in these cases may be associated with the virulence of a putative exciting agent or with the immune response genes.

We thank Dr B. M. Ansell and Dr E. B. Raftery for their co-operation and advice in the preparation of this paper.

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British Heart Journal, 1979, **42**, 231-242

Proceedings of the British Cardiac Society

THE 58TH ANNUAL GENERAL MEETING of the British Cardiac Society was held at the Medical and Biological Sciences Building of the University of Southampton on Wednesday and Thursday, 4 and 5 April 1979. The President, W. SOMERVILLE, took the Chair during private business. At the scientific sessions the Chair was taken by A. M. JOHNSON.

Abstracts of papers

Coronary artery disease in the transplanted heart: failure to develop abnormal lactate metabolism on atrial pacing

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Accelerated coronary artery disease is a frequent problem in the transplated heart. As the patient with a denervated heart cannot experience angina, it is difficult to judge the clinical significance of advanced coronary artery disease. Abnormal lactate metabolism after atrial pacing has been shown reliably to reflect 2 or 3 vessel coronary artery disease. We therefore performed atrial pacing and coronary sinus lactate studies in 6 cardiac transplant recipients in an attempt to determine objectively the presence or absence of myocardial ischaemia. Coronary angiography was performed in all 6 patients, 3 of whom had advanced coronary artery disease and 3 normal coronary arteries. Pacing was at 160 beats/minute for at least 10 minutes with 12-lead electrocardiograph monitoring of the ST segment. All studies were without complications and symptoms.

All 6 patients had normal lactate metabolism on peak pacing as judged by the absence of lactate production and an extraction ratio greater than 10 per cent. Of the 3 patients with coronary artery disease, 2 subsequently underwent retransplantation, 1 for cardiac failure and the other for massive myocardial infarction.

The transplanted heart with advanced coronary artery disease appears unable to develop abnormal lactate metabolism on atrial pacing. The mechanism is unclear, but may reflect loss of sympathetic innervation.

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Ambulatory ST segment monitoring: problems, pitfalls, and solutions

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Ambulatory tape recording systems which are suitable for detection of arrhythmias are not adequate for accurate detection and quantification of ST segment shift. Low frequency artefact and baseline drift are major problems. Systematic investigation has resulted in recommendations for skin preparation and a new electrode design which minimises connection artefacts. Three tape recorders used for signal storage have been evaluated: the Medilog Mark I, the Cardiodyne real-time sampling recorder, and the Medilog Mark II. High fidelity electrocardiographs were recorded during and after exercise in 20 patients with ischaemic heart disease using the Marquette CASE system and the 3 recorders simultaneously. The taped recordings were compared with the CASE recording as a standard. Medilog I showed distorted calibration signals, unpredictable ST depression, and slope distortion and baseline drift. Medilog II had good calibration with a stable baseline and excellent ST reproducibility. The best reproduction was obtained with the Cardiodyne. Similar results were obtained from 24-hour ambulatory outpatient records in the same patients. Accurate and repeatable ST segment deviations can only be obtained by using an electrode system which gives a stable signal and a recorder whose physical characteristics are adequate. This new electrode system will give reliable records with Medilog II (24 hours) and the Cardiodyne (28 s in 15 min) but not with the Medilog I.

Effects of propranolol on left ventricular wall movement in patients with ischaemic heart disease

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In order to assess the effects of propranolol on left ventricular wall movement in ischaemic heart disease, simultaneous echo-, phono-, and apex cardiograms were recorded and digitised in 16 patients before and after 0·1 mg/kg iv, or therapeutic oral dose for 1 week. In 9 (group A) contraction was synchronous, and in 7 (group B) there was evidence of incoordinate wall movement. There were small reductions in heart rate, peak VCF, and extent of dimension change ($P < 0\cdot05$ for each). In group A, the main abnormality was a 80 ms reduction in the duration of inward wall movement so that minimum dimension occurred prematurely with respect to mitral valve opening. Diastolic events were otherwise unaltered. In group B, apex-dimension relations and timing of A2 and mitral valve opening were abnormal under control conditions, and minimum dimension already occurred prematurely. Propranolol did not alter systolic events further, but aggravated diastolic abnormalities with further delay in mitral valve opening ($P < 0\cdot001$), 'O' point ($P < 0\cdot01$), prolongation of isovolumic relaxation ($P < 0\cdot01$), and reduced rate of dimension increase ($P < 0\cdot05$).

In ischaemic heart disease, therefore, the effect of propranolol administration is significantly modified by the presence of incoordinate contraction in a manner not predictable from the results in normal subjects.

Abnormal aortic valve echoes in mitral prolapse

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Abnormal aortic valve echograms were recorded in 6 patients with echocardiographic and clinical evidence of mitral prolapse.

No patient was considered to have Marfan's syndrome: 2 had clinical signs of mild aortic regurgitation but in the remaining patients, including 1 who subsequently had a myxomatous aortic valve replaced, aortic valve disease was not suspected clinically.

On cross-sectional echocardiograms, the aortic valve cusps appeared thickened but mobile. Three cusps were defined in each of the 4 valves imaged in transverse section.

M-mode scans showed normal motion of the aortic cusps in systole but during diastole multiple echoes were recorded from the cusps in the centre of the aortic root. There was evidence of aortic root dilatation in 2 patients.

It is suggested that the echocardiographic features described reflect myxomatous degeneration of the aortic valve, and it is recommended that the investigation of patients with mitral prolapse should include echocardiographic assessment of the aortic valve.

Plasma noradrenaline concentrations during isometric and dynamic exercise in essential hypertension

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Plasma noradrenaline concentrations were studied in 15 essential hypertensives, before, during, and after isometric and dynamic exercise. Blood pressures were measured intra-arterially from the brachial artery. Isometric exercise comprised maximum grip strength for 30 seconds followed by 30 per cent of maximum for up to 4 minutes 30 seconds. The same subjects later performed dynamic exercise on a bicycle ergometer.

Resting arterial pressure, heart rate, and plasma noradrenaline were similar before each period of exercise. Mean arterial pressure increased by 29·1 to 144·6 ± 23·6 mmHg during isometric exercise ($P < 0\cdot001$) and to 150 ± 25·4 mmHg during bicycling ($P < 0\cdot001$).

Heart rate increased by 23 to 96·6 ± 13·5 bpm during isometric exercise ($P < 0\cdot001$) and to 126·7 ± 16·3 bpm during bicycling ($P < 0\cdot001$). Plasma noradrenaline concentration did not alter significantly during isometric exercise, increasing from 3704·4 ± 1196·8 pmol/l (626·8 ± 202·5 pg/ml) to 3949·1 ± 1341 pmol/l (668·2 ± 226·9 pg/ml), but rose from 3198·5 ± 843·4 pmol/l (541·2 ± 142·7 pg/ml) to 7705·6 ± 3212·1 pmol/l (1303·8 ± 543·5 pg/ml) during dynamic exercise ($P < 0\cdot001$).

Noradrenaline increased more during dynamic exercise for the same mean pressure rise (heart rate was higher however). Previous observations of raised plasma noradrenaline during isometric exercise in patients with disturbed left ventricular function do not seem to apply to hypertensive subjects not in failure.

Computerised dichromatic earpiece densitometer for measurement of cardiac output

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Technical problems have prevented the routine use of earpice densitometry to measure cardiac output. We have evaluated a precalibrated, computerised, dichromatic earpiece densitometer by comparison of cardiac output with that simultaneously determined using a cuvette densitometer. Correction for ear blood content and background dye for the individual patient used a 'bloodless ear' technique.

Thirty-four patients were studied during diagnostic cardiac catheterisation. Cardiac output was determined after duplicate injections of indocyanine green in the main pulmonary artery and in the femoral vein. In 4 patients with low cardiac outputs the dilution curves were unacceptable. For the remaining 30 patients measured cardiac output was in the range 2·20 to 7·15 l/min. Comparison of computer and manual processing of the dye dilution curves showed excellent agreement (r 0·994; SD 1·47%). Reproducibility of cardiac output measurements by earpiece densitometry (SD 5·2%) was comparable with that using the cuvette (SD 5·3%). Comparison of simultaneously determined cardiac output using both instruments showed good correlation (r 0·83; SD 7·2%) after pulmonary arterial injection of dye and (r 0·78; SD 8·3%) after femoral venous injection.

The instrument offers a useful technique for the non-invasive measurement of cardiac output at rest. Further applications are being studied.

Relation between symptoms and arrhythmias in patients with sick sinus syndrome

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The relation between symptoms and documented arrhythmias has been studied in 94 patients with sick sinus syndrome (mean age 67·6 years). 22 patients were being treated medically, 32 had implanted cardiac pacemarkers, and the remaining 40 were assessed both before and after pacemaker implantation.

Documented arrhythmias were grouped into 5 categories: (a) major atrial arrhythmias; (b) major ventricular arrhythmias; (c) profound bradycardia; (d) minor atrial or ventricular arrhythmias including minor bradycardia; (e) normal sinus thythm.

Of the patients treated medically, 76 per cent experienced major atrial arrhythmias and 97 per cent of these caused symptoms, 32 per cent of these patients had major ventricular arrhythmias apart from bradycardia; 82 per cent had major bradycardia and the great majority of both fast and slow ventricular arrhythmias correlated with symptoms. Only 29 per cent of the minor arrhythmias were associated with symptoms.

Of this medical group, 19 per cent complained of symptoms despite 24-hour electrocardiograms showing only stable sinus rhythm. The incidence of arrhythmias in patients with pacemakers was very much lower for both major atrial arrhythmias (33%) and major ventricular arrhythmias (12·8%). When such arrhythmias did occur about two-thirds of the patients had associated symptoms.

In the third group of patients implantation of a pacemaker reduced the incidence of symptoms to approximately one-third of the previous level and this occurred for all types of arrhythmia. It was apparent that arrhythmias in all categories a–d diminished spontaneously during sleep.

We conclude that there is only fair correlation between the patients' symptoms and the documented arrhythmias; the correlation is best for profound bradycardia and rapid atrial arrhythmias. Implantation of a cardiac pacemaker considerably reduces the subjective complaints associated with both fast and slow arrhythmias.

Prognosis in sinuatrial disorder (sick sinus syndrome)

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The 5-year survival rate in patients with sinuatrial disorder has been compared with that of the general population. The relative risk of mortality has been assessed according to the severity of the disease and whether or not a pacemaker was implanted.

Over a period of 10 years 386 patients were collected from the Devon Heart Block Survey. All had a chronic sinus bradycardia and were classed as either group 1 if there were additional major electrocardiographic changes ($N = 160$) or group 2 if there was uncomplicated sinus bradycardia ($N = 226$).

The mortality in the 2 groups was similar in the 5 years after entering the survey. In addition there was no significant difference in the relative risk of mortality as compared with a general population matched for age and sex, that is,

$$\frac{\text{Proportion dead in sample}}{\text{Proportion dead in population}} = 0{\cdot}39,\ 1{\cdot}04,\ 0{\cdot}87,\ 0{\cdot}86,\ 0{\cdot}89$$

over the first 5 years. Survival of the 61 paced patients was no different from that of the unpaced patients in either group.

It is concluded that survival of these patients with chronic sinuatrial disorder is similar to that of the general population and does not appear to be materially altered by pacemaker implantation.

Study to determine normal fetal heart rate and rhythm

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The fetal heart was recorded for 5 minutes onto cassette from 963 randomly selected mothers between 36 weeks gestation and term. The recordings were printed as phonocardiograms and analysed directly by listening to rhythm and measuring rate. Twelve fetuses (1%) had premature beats ranging from 3 to 102 per 5 minute recording. Episodes of bradycardia, rate 70 to 110/minute ranging from 3 to 25 seconds duration, occurred in 18 (1·9%). Episodes of bradycardia (± 70/minute) ranging from 5 seconds to 5 minutes duration, occurred in 7 (0·7%). Episodes of tachycardia (> 180/minute) ranging from 30 to 90 seconds in duration occurred in 5 (0·5%). Recordings were replayed through a standard antepartum fetal heart rate monitor. All of the premature beats, 11 of the 18 fetal heart rates between 70 and 110/minute, 5 of the 7 rates below 70/minute, and 2 of the 5 rates over 180/minute were not detected. These failures of standard monitors to detect the majority of rhythm and rate changes in the fetus are the result of an inbuilt electronic circuit evolved to avoid artefact. This lost information could be relevant to hitherto unexplained antepartum asphyxia and intrauterine death.

Study of heart rate and rhythm in normal schoolchildren

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Cardiac arrhythmias associated with sinus node dysfunction have been suggested as a cause of fits, faints, and funny turns in childhood. However, information on normal heart rate and rhythm is poorly documented and therefore single 24-hour electrocardiographic recordings were performed on 90 randomly selected healthy 7 to 11-year-old children. The mean highest heart rate over 9 beats was 164 ± 16, the mean lowest heart rates were 49 ± 6 over 3 beats, and 56 ± 6 over 9 beats duration. At their lowest heart rates, 42 (46%) had intermittent junctional rhythms. One child had episodes of complete 2:1 Wenckebach atrioventricular nodal block and 7 had intermittent prolongation of the PR interval (> 0·20 s). Nineteen had isolated atrial premature beats. In a randomly selected subgroup of 29 children, 23 (79%) had sinatrial Wenckebach block and 5 (17%) had 2:1 sinatrial block patterns.

A history and clinical examination were taken on all children studied and these showed no correlation between variations in rhythm and rate and clinical findings. This study shows that normal children have variations in heart rate and rhythm hitherto considered to be abnormal and, therefore, must be carefully considered before making a diagnosis of conducting system disorders such as the sick sinus syndrome.

Comparison between results of primary repair of large ventricular septal defects before and after the age of 1 year

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Forty-five patients with large ventricular septal defects and a pulmonary artery pressure in excess of 0·75 of systemic pressure have undergone primary closure of their defect. Twenty-nine patients were under the age of 1 year (group A) and 16 patients were over 1 year (group B). Preoperatively the pulmonary vascular resistance was 1·5 to 6 units in group A and 2 to 8·5 units in group B. There were 2 early deaths in group A and no late deaths in either group. Follow-up was from 9 to 92 months (mean 40 months). All children are asymptomatic, though 1 child in group B is on cardiac drugs. Eighteen patients have been investigated 1 to 4 years after operation in group A and 9 patients, 9 months to 7 years after operation in group B. There were no residual shunts in either group. The peak pulmonary artery pressure was less than 25 mmHg at rest and on exercise in all 18 patients in group A, while in group B only 1 patient had a normal pulmonary artery pressure at rest while in 8 patients the pulmonary artery/systemic ratio was 0·33 and 0·6, even at rest. The pulmonary vascular resistance was 2 units, or less, in all patients in group A and 1·5 to 6 units in group B. Right ventricular end-diastolic pressure at rest was below 10 mmHg in both groups. Left ventricular ejection fraction was between 65 to 85 per cent in group A and 55 to 75 per cent in group B.

It is concluded that the late results of primary correction of large ventricular septal defects in infancy are significantly better than those in older children.

Total correction of tetralogy of Fallot in adult life—a worthwhile operation?

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Between October 1969 and September 1978, 18 patients between the ages of 16 and 50 years (mean 25·5 years) underwent total correction of tetralogy of Fallot. All patients were operated upon because of recent deterioration in symptoms. Seven patients had had previous palliative operations in childhood and 2 had had attempts at total correction in other centres. Severe tricuspid regurgitation was present in 1 and triple coronary artery disease in 1. Three patients had reconstruction of the right ventricular outflow tract with a single cusp of a fresh aortic homograft. Additional triple aortocoronary vein grafts were performed in 1 and resection of a left ventricular diverticulum in 1. There were no early or late deaths. The patients have been followed up for between 4 and 111 months (mean 43 months) and have had considerable symptomatic improvement. Five patients have been restudied 1 to 3 months after operation and all have LV/RV ratios of less than 0·45 with evidence of improved left ventricular function.

It is concluded that total correction of tetralogy of Fallot in adult life can be carried out safely and can lead to considerable symptomatic improvement.

Underdeveloped right ventricle with right-to-left shunting interatrial defect: recognition and results of surgery

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Studies were made on 7 patients, 3 to 19 years of age, with cyanosis caused by right-to-left shunts at atrial level and hypoplastic abnormalities of the right ventricle. Common clinical features were cyanosis, clubbing, giant 'a' wave, quiet parasternal area, soft systolic murmur, inspiratory third and/or atrial sound, close second sound, right atrial prominence on electrocardiogram, and radiograph with pulmonary oligaemia. Cyanosis was progressive. Investigation confirmed shunting with arterial oxygen saturations of 82 to 95 per cent at rest, falling to 80 to 91 per cent with effort, raised right ventricular end-diastolic pressures, and tricuspid valve gradients in 4. Right ventricular angiographic appearances were bizarre, with reduced ejection, small tricuspid ring, smooth inflow, and multiple pouches. The shunt was closed in 4, in 1 the dominant lesion proved to be an abnormal adherent Eustachian valve above the small tricuspid ring. Early postoperative problems included right heart failure in all and arrhythmias in 2. All are well 6 months to 3 years later.

Of the 7 patients, 5 had family histories of congenital abnormalities. Three presented with an incorrect diagnosis of inoperable Eisenmenger. Diagnostic accuracy is essential since surgery may abolish cyanosis, and the long-term outlook may be good if operation is carried out early enough to allow the right ventricle to develop normally and prevent irreversible hypoplasia.

Mechanism of sudden death in postoperative tetralogy of Fallot

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Late sudden death occurs after the correction of tetralogy of Fallot in 1 to 3 per cent of patients, The mechanism is controversial: conduction disturbances progressing to complete heart block or serious ventricular arrhythmia have been suggested. We reviewed the pre-, perioperative, and follow-up electrocardiograms of 176 patients after correction of tetralogy of Fallot age 3-16, mean 8 years, for evidence of conduction disturbances and arrhythmia. 24-hour ambulatory electrocardiographic monitoring was performed in 65 patients.

Perioperative electrocardiograms showed complete right bundle-branch block in 83 per cent, and right bundle-branch block and left anterior hemiblock in 9 per cent, trifascicular block in 3 per cent, and mean frontal QRS axis shift greater than 90 degrees in 16 per cent. Seven patients died perioperatively: 2 had complete heart block and 2 had frequent ventricular extrasystoles. Transient perioperative arrhythmias were: complete heart block in 8 patients, frequent ventricular extrasystoles in 14 patients, ventricular fibrillation in 1 patient.

Follow-up was 1 to 20 years (mean 12 years). There were 5 late sudden deaths; none of these patients had documented perioperative arrhythmias or conduction disturbances. During follow-up, the electrocardiogram showed a progressive axis shift with development of left anterior hemiblock in 12 per cent of patients, 2 of the sudden deaths occurring in this group. 24-hour ambulatory electrocardiograms showed 4 patients (6%) with episodes of supraventricular tachycardia, 19 patients (30%) with frequent multiform or coupled ventricular extrasystoles, 8 patients (12%) with intermittent first degree heart block, 4 patients with atrioventricular dissociation, and 10 patients (15%) with sinus pauses. The high frequency of ventricular arrhythmia was not confined to the early postoperative or late left anterior hemiblock groups.

We have shown a high incidence of late electrocardiographic axis shift with development of left anterior hemiblock associated with sudden death. This may represent progressive conduction disease, and this group may be at particular risk from ventricular arrhythmia and complete heart block.

Amiodarone in management of chronic refractory ventricular tachycardia

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Previous reports have shown the efficacy of the drug amiodarone in the management of atrial arrhythmias especially atrial fibrillation associated with the Wolff-Parkinson-White syndrome: it has been less effective against reciprocating atrioventricular tachycardias associated with the Wolff-Parkinson-White syndrome and paroxysmal atrioventricular node re-entry. We have studied its effects in 10 patients (aged 24 to 61 years) with recurrent ventricular tachycardia refractory to all conventional drug treatment (duration of symptoms 6 to 48 months). Seven patients had required repeated electroversions. Eight patients were studied electrophysiologically using programmed stimulation before amiodarone (5 re-entry and 3 focal mechanism). Ambulatory electrocardiographic monitoring was performed both before and serially during subsequent treatment with amiodarone. (Follow-up 4 to 16 months, mean 10 months.)

Six patients (congestive cardiomyopathy, 3: ventricular aneurysm, 2: idiopathic ventricular tachycardia, 1) were asymptomatic on amiodarone with no ventricular tachycardia on ambulatory electrocardiographic monitoring. There was also pronounced reduction in the number of ventricular premature beats. The average maintenance dose was 200 mg per day. Three patients (old infarct, 1; mitral valve prolapse, 2) were improved with only either short runs of ventricular tachycardia or frequent premature beats on ambulatory electrocardiographic monitoring. Maintenance dosage was between 300 and 600 mg per day for these patients. One patient with congestive cardiomyopathy and re-entrant left ventricular tachycardia showed no improvement on 600 mg of amiodarone per day. One patient had ocular side-effects of treatment which settled on reducing the dose without loss of antiarrhythmic effect.

We conclude that amiodarone has an important place in the management of chronic refractory ventricular tachycardia.

Treatment of resistant non-ischaemic ventricular tachycardia

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When ventricular tachycardia fails to be controlled by one of the wide variety of drugs available, the disabling symptoms and inherent dangers require that alternative methods of treatment be sought. We describe 2 patients with ventricular tachycardia not caused by cardiac ischaemia in whom surgery was required. The surface electrocardiogram of a patient with mitral valve prolapse suggested that the tachycardia arose from a region of the ventricle closely related to the mitral valve; haemodynamically unimportant mitral regurgitation in sinus rhythm assumed major haemodynamic importance during tachycardia. Epicardial mapping at operation showed the tachycardia to be closely related to the posterior papillary muscle; after mitral valve replacement the patient is free of arrhythmias. In a second case the development of a ventricular aneurysm after non-penetrating cardiac trauma was associated several years later with frequent incapacitating episodes of ventricular tachycardia. Cryoablation after epicardial mapping has completely abolished these episodes. The follow-up in both these cases now exceeds 18 months.

These 2 patients illustrate the importance of accurately identifying the underlying cause of any resistant ventricular tachycardia. Epicardial mapping with surgical ablation may be the only means of control of such an arrhythmia in patients who fail to respond to drug treatment.

Relation between sites of ventricular tachycardia and underlying ventricular disease: implications for therapy

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The relation between the site of ventricular tachycardia, and of any underlying ventricular disease was examined in 38 patients with chronic recurrent ventricular tachycardia. The arrhythmia was localised in each case from its electrocardiographic appearance in all 12 conventional surface leads. Transvenous intracardiac mapping was also used in 28, as was direct mapping during cardiac surgery in 11. Ventricular disease was localised angiographically and sometimes also by nuclear and echocardiography. In 21 patients with coronary artery disease, chronic recurrent ventricular tachycardia arose from sites of prior myocardial infarction in 20. Fourteen of these had a ventricular aneurysm. The remaining patient with high septal chronic recurrent ventricular tachycardia had non-corresponding myocardial infarction but critical stenosing coronary artery disease in the 2 vessels supplying the apprently undamaged septum. Bypass grafting failed to abolish the chronic recurrent ventricular tachycardia.

While a causal relation was probable in 7 with congestive cardiomyopathy, the site of chronic recurrent ventricular tachycardia was very variable and was not associated with localised disease. In 4 patients with mitral valve prolapse, chronic recurrent ventricular tachycardia was localised to, but not specific for, this abnormality. In 2 patients with surgically corrected tetralogy of Fallot, chronic recurrent ventricular tachycardia arose from the region of the pulmonary outflow tract in 1, and from the lower anterior septum in the other. One patient with both idiopathic left ventricular aneurysm and aortic valve disease had chronic recurrent ventricular tachycardia not associated with either. The focus was successfully localised and ablated after both aortic valve surgery and aneurysmectomy had failed. Three had idiopathic chronic recurrent ventricular tachycardia all arising from the right ventricular anterior free wall.

We conclude that the localisation of ventricular tachycardia using 12 lead surface electrography is both valid and useful in the management of such arrhythmias.

Response of paroxysmal atrial flutter to intravenous disopyramide phosphate and overdrive atrial pacing

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Ten patients with spontaneous paroxysmal atrial flutter were investigated electrophysiologically. Three had Wolff-Parkinson-White syndrome, 3 Lown-Ganong-Levine syndrome, and 1 had concealed Wolff-Parkinson-White. Paroxysmal atrial flutter was initiated by right atrial pacing and electrograms from the right atrium and coronary sinus were observed for 5 minutes to ensure stable biatrial flutter.

Paroxysmal atrial flutter was terminated by 10 second bursts of right atrial pacing at rates 10 to 100 bpm faster than its intrinsic rate in only 2 patients. Paroxysmal atrial flutter (reinitiated in 2 patients) was then treated with intravenous disopyramide phosphate, 2 mg/kg body weight, infused over 5 minutes. In all 10 patients the atrial rate slowed from 320 ± 43 bpm to 217 ± 27 bpm ($P < 0{\cdot}001$) and paroxysmal atrial flutter terminated in 1. Though the mean ventricular rate fell from 158 ± 54 bpm to 144 ± 47 bpm (NS) atrioventricular conduction block decreased and left 2 patients with higher ventricular rates. In 9 patients right atrial pacing, repeated after disopyramide phosphate, terminated 7 arrhythmias. In 1 patient right atrial pacing was successful before but not after disopyramide phosphate.

In this study right atrial pacing and disopyramide phosphate, singly and in combination, terminated paroxysmal atrial flutter in 9 of the 10 patients and it is suggested that this combination reduces the need to proceed to DC cardioversion.

Comparison of atrial arrhythmias with atrial stimulation threshold and conduction times in patients with sick sinus syndrome

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Thirty-two patients have been investigated by repeated 24-hour electrocardiographic monitoring and also by measurements of atrial and ventricular stimulation thresholds. Intra-atrial conduction time was also measured in 2 ways: (1) as the maximum P wave duration recorded on multiple lead surface electrocardiograms with a rapid paper speed, (2) as delay between recordings from the high right atrium (near the sinus node) and the low right atrium (near the tricuspid ring).

Patients with atrial enlargement detected either by electrocardiogram or by echocardiogram were excluded. Of the 32 patients, 10 were normal controls, 10 had complete heart block, and 12 had sick sinus syndrome.

Of the patients with sick sinus syndrome 83·3 per cent had atrial arrhythmias as opposed to 30 per cent of patients with complete heart block and 10 per cent of patients with normal sinus rhythm.

Intra-atrial conduction time was significantly longer in patients with sick sinus syndrome than in those with complete heart block or normal sinus rhythm ($P < 0{\cdot}001$).

The stimulation threshold in the atrium, with a 1 ms impulse and a C51 electrode was 2·2V for patients with sick sinus syndrome, 1·25V for patients with complete heart block, and 0·9V for normal subjects. The ventricular stimulation thresholds in the same groups were 0·62V, 0·55V, and 0·58V, respectively. All values are means of the 3 lowest readings obtained.

There was a close correlation between patients with sick sinus syndrome who had frequent atrial arrhythmias, prolonged intra-atrial conduction times, and high atrial stimulation thresholds. These 3 findings are regarded as indicating the extent of atrial disease, and, though the incidence of such abnormalities was much lower in the patients with complete heart block, this group also had evidence of atrial involvement. The information is of clinical significance when physiological pacing is being considered.

Electrophysiological properties of nifedipine in comparison with those of verapamil

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We have investigated the electrophysiological properties of nifedipine, a dihydropyridine derivative which has potent effects on the slow inward (calcium-dependent) channels of smooth and cardiac muscle and is an effective anti-anginal agent. Twelve patients underwent electrophysiological testing to determine the nature of their arrhythmias. Seven were shown to have paroxysmal reciprocating atrioventricular tachycardia associated with the Wolff-Parkinson-White syndrome. Four patients had either paroxysmal atrial fibrillation or flutter and 1 had sinus node disease. Nifedipine (7·5 μg/kg body weight) was administered over 3 minutes during paroxysmal reciprocating atrioventricular tachycardia or during rapid atrial pacing with 1:1 atrioventricular conduction. In no instance was paroxysmal reciprocating atrioventricular tachycardia terminated nor did 2nd degree atrioventricular block occur in those patients who were being paced.

Electrophysiological indices were measured again 5, 10, and 20 minutes after administration. The only significant change was an increase in the sinus rate presumably because of altered autonomic balance resulting from the negative inotropic action. No change was observed in the functional or effective refractory periods of the atrioventricular node; in contrast, verapamil (0·15 mg/kg) subsequently given to all patients consistently terminated paroxysmal reciprocating atrioventricular tachycardia and lengthened atrioventricular nodal refractoriness (functional or effective refractory periods).

Nifedipine is a potent 'calcium-antagonist' but does not possess the antiarrhythmic actions of some similar agents. While it appears safe to combine nifedipine with beta-blockers, these results raise the possibility that there may be more than one type of slow inward (calcium-dependent) channel in cardiac cell membranes.

Effect of variation in coronary artery anatomy on distribution of stenotic lesions

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The influence of 3 aspects of coronary artery anatomy (length of left main coronary artery, angle of bifurcation into anterior descending and circumflex branches, and artery of dominance) was investigated by review of 154 consecutive coronary angiograms. Ninety-five had critical stenoses ($\geq 50\%$ luminal diameter).

The mean left main coronary artery length in diseased arteries (10·6 mm) was shorter ($P < 0{\cdot}50$) than in normals (12·9 mm). Proximal lesions were associated with much shorter left mainstems (9·1 mm) than distal ones (12·9 mm) ($P < 0{\cdot}005$).

There was no difference in the mean angle of bifurcation either between angiograms with (81°) and without (75°) stenoses ($P > 0{\cdot}05$) or between proximal (85°) and distal (76°) disease groups ($P > 0.1$). In combination with mainstem length, a wide bifurcation angle exerted a slight ($0{\cdot}05 < P < 0{\cdot}1$) additional influence favouring proximal localisation.

Dominant circumflex artery systems possessed mean left main coronary arteries (9·1 mm) significantly shorter ($P < 0{\cdot}05$) than right coronary artery dominant ones (12·0 mm) but both had identical disease distribution.

Short left main coronary arteries favour proximal localisation of stenoses. The angle of bifurcation alone exerted no influence but in combination with a short left main coronary artery a wide angle slightly enhanced proximal distribution. The poor prognosis of proximal lesions and their suitability for bypass grafting make these relations important.

Experimental investigation of arteriographic findings that suggest coronary spasm

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Experiments were undertaken in anaesthetised dogs to test the hypothesis that transient narrowing or disappearance of a coronary artery during arteriography may not necessarily be the result of coronary spasm. The left anterior descending coronary artery was narrowed in open and closed chest experiments. Atrial pacing (in 5) and ergonovine maleate, 0·4 mg (in 5) were then used to produce acute regional myocardial ischaemia. Simultaneous left ventricular and left coronary angiograms were recorded before and after stenosis of the left anterior descending artery and then during ischaemia. Intravenous glyceryl trinitrate (10 μg/ml per min) was then infused and the angiograms repeated. In a further 5 dogs an injection of microspheres into the left anterior descending artery alone was used to produce regional ischaemia. In all the dogs the left anterior descending artery was opacified throughout its length before and after stenosis with no evidence of regional ischaemia. During regional ischaemia the portion of the left anterior descending artery associated with the dyskinetic segment failed to opacify. This was reversed by using intravenous glyceryl trinitrate. The same experiments using stenosis of the left anterior descending artery and atrial pacing were performed in 10 dogs while assessing changes in regional myocardial perfusion using krypton-81 m and a gamma camera. Atrial pacing produced a redistribution of perfusion with a 78 ± 14 per cent decrease in blood flow in the affected segment. This study suggests that haemodynamic and mechanical factors that affect coronary flow during acute regional ischaemia can cause the transient narrowing or disappearance of a coronary artery. The angiographer should consider that the arteriographic appearances of the coronary arteries may be temporarily changed during episodes of acute regional myocardial ischaemia with altered ventricular function.

Evidence for enhanced heart rate response to repeated treadmill testing uninfluenced by propranolol in stable angina

M. Joy, C. Pollard, and T. O. Nunan
St. Peter's Hospital, Chertsey, Surrey

Nine normotensive male patients with stable angina, no previous history of myocardial infarction, a normal chest *x*-ray film and resting electrocardiogram, but with a positive electrocardiographic response to exercise were studied. Each patient underwent Bruce procedure treadmill electrocardiography at 0800, 1200, and 1600 hours on one day, the end-point being angina or exhaustion. The maximal and recovery heart rates were significantly greater in the afternoon than in the morning ($P < 0{\cdot}025$) and the ST segment changes were still significantly greater ($P < {\cdot}002$) after 10 minutes recovery, in spite of comparable walking times. In 9 normal subjects there was no such diurnal variation in exercise response.

Nine further patients who had been receiving propranolol 40 mg qds for at least a month were studied in a similar way and received their medication after each treadmill trip. There was no significant difference in the mean age, weight, or serum cholesterol between the two groups. The treated group also had higher afternoon maximal and recovery heart rates which were significantly greater until 3 minutes into the recovery period ($P < 0{\cdot}025$), but the ST segment changes were greater only until the end of the first minute ($P < 0{\cdot}05$). When the treated group was retested the same effect was shown and the results were also valid tested diagonally across the interval which was 6 weeks. Possible mechanisms and the implications of these observations were discussed.

Biochemical effects of beta$_2$ adrenergic blockade in patients undergoing cardiopulmonary bypass

M. C. Petch, R. McKay, and D. W. Bethune
Papworth Hospital, Papworth Everard,
Cambridge

In a previous retrospective study a paradoxical rise in serum potassium during cardiopulmonary bypass was observed in patients taking propranolol or oxprenolol. A prospective comparison of propranolol with the beta$_1$ adrenergic antagonist metroprolol was therefore undertaken in patients undergoing surgery for coronary artery disease. The 10 patients in each group were comparable with respect to age, duration of symptoms, etc, and both groups were managed according to a strict procedure. Propranolol or metoprolol was continued until surgery and no blood or potassium supplements were administered during the study. Mean serum potassium rose by 1·2 mmol/l during cardiopulmonary bypass in the propranolol group and fell by 0·08 mmol/l in the metoprolol group ($P \neq < 0{\cdot}001$). Urinary potassium loss was similar in both groups. After an initial glucose load serum glucose level fell significantly in the propranolol group as compared with the metoprolol group.

Disturbances of potassium homeostasis after beta$_2$ blockade have been shown in animal experiments and our results indicate a relation between beta$_2$ blockade and hyperkalaemia during cardiopulmonary bypass; this may be associated with intracellular substrate deficiency and subsequent myocardial failure.

Potential protective value of enhanced myocardial carbohydrate utilisation with reduced free fatty acid uptake after UK 25842 in patients with coronary artery disease

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N. Jackson, and D. E. Jewitt
Cardiac Department, King's College Hospital,
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The influence of UK 25842 (L-4-hydroxyphenylglycine) in a dose of 4 to 12 mg/kg body weight on haemodynamics and myocardial metabolism was investigated in 20 patients with obstructive coronary artery disease before and during angina pectoris induced by atrial pacing. Heart rate, intracardiac pressures, cardiac output, and coronary venous blood flow were measured. Myocardial uptake and extraction of lactate, pyruvate, free fatty acids, acetoacetate, glycerol, and triglycerides were determined from systemic arterial and coronary sinus blood samples.

No major haemodynamic changes or any side effects occurred after UK 25842. Atrial pacing time to the onset of angina increased from 211 ± 29 to 290 ± 27 seconds after 12 mg/kg UK 25842.

Both myocardial free fatty acid uptake and extraction ratios fell. During angina myocardial free fatty acid uptake was reduced from 31·5 ± 6·3 to 17·4 ± 4·8 μmol/min. ($P < 0{\cdot}05$). There was a corresponding increase in myocardial uptake of lactate of −25·5 to +14·4 μmol/min (−2·3 to +1·3 mg/min) and of pyruvate of 2·3 to 13·7 μmol/min (0·2 to 1·2 mg/min), $P < 0{\cdot}01$, with reversal of lactate production in 60 per cent of patients. Myocardial glucose uptake also increased. This change from free fatty acid to carbohydrate utilisation by the myocardium was confirmed by an increase in the myocardial RQ from 0·8 to 1·02. These changes were associated with a reduction in myocardial oxygen consumption (MVo$_2$) from 23·5 to 19·9 ml/min.

This reduction in MVo$_2$ associated with enhanced myocardial carbohydrate utilisation, produced by UK 25842, has great potential value not only in patients with angina but also in those with myocardial infarction, when jeopardised areas of the myocardium may be salvaged.

Cardiac emission tomography with thallium 201: new approach to perfusion scintigraphy

D. S. Dymond, D. L. Stone, A. T. Elliott,
K. E. Britton, and R. A. J. Spurrell
Departments of Cardiology and of Nuclear
Medicine, St. Bartholomew's Hospital,
London EC1A 7BE

This report describes the use of a new device for myocardial imaging in humans by emission computerised tomography. The dual-detector emission tomograph rotates in 6 degree increments, at each of which a 40 cm linear scan is performed. A total of 30 rotations complete a single scan, taking between 4 and 15 minutes. The slice image is reconstructed into an 80 × 80 matrix.

The tomograph has been used to image the distribution of thallium 201 in a group including normals, patients with left ventricular aneurysms, patients with myocardial infarction, and patients with chest pain. All patients have been studied both by conventional gamma camera imaging (4 projections), and by emission computerised tomography (average of 3 transverse sections).

Patients with chest pain were injected after exercise and were studied both initially and after a 4-hour delay to permit redistribution. The remainder were studied only at rest. The initial results have indicated that exercise perfusion defects not seen on the conventional images can be unmasked by emission computerised tomography. The spatial separation between the liver and spleen and the heart on the image may yield superior results in the assessment of apical perfusion defects. The addition of depth information may lead to improved scintigraphic assessment of infarct size and allow detection of subendocardial ischaemic zones.

Pulmonary perfusion imaging applied to prediction of pulmonary vascular pressures

D. N. F. Harris, D. M. Ackery, and N. Conway
Southampton University Hospitals, Hampshire

The effect of gravity on pulmonary blood flow is well established. Normally the lung bases are better perfused than the upper zones but this difference disappears as left atrial pressure rises. Theoretically radionuclide lung imaging should reflect this change quantitatively but previous attempts to show this have met with mixed success. We have investigated 30 patients with valvar heart disease undergoing cardiac catheterisation and have used a new radionuclide method. Perfusion images were recorded in anterior and posterior views. On the computer, counts from the upper half (UZ) and the total (T) of the images were made and the geometric mean of the two views calculated to give composite UZ and T counts. The ratio UZ/T was plotted against mean pulmonary wedge pressure (MPWP) and mean pulmonary artery pressure (MPAP). Good correlation was found between UZ/T and MPWP ($r = 0{\cdot}95$); correlation with MPAP was less satisfactory ($r = 0{\cdot}72$). The data include those from 4 patients studied both before and after corrective surgery (with postoperative cardiac catheterisation) when the change in the UZ/T ratio reflected the reduction in MPWP achieved. This simply-obtained non-invasive measurement may be used as a reliable index of the height of MPWP diagnostically, and for sequential studies.

Quantitative thallium 201 myocardial imaging in coronary artery disease

P. S. Robinson, A. Crowther, B. S. Jenkins, M. M. Webb-Peploe, D. N. Croft, and D. J. Coltart
Department of Cardiology, St. Thomas' Hospital, London SE1 7EH

Myocardial imaging using thallium 201 (^{201}Tl) was performed in 60 subjects who achieved predicted maximal exercise performance without evidence of cardiovascular abnormality. Computer processing of the images was carried out to provide quantitative information on regional myocardial ^{201}Tl distribution, and 'normal' variation was determined.

This processing technique was applied to rest and exercise ^{201}Tl myocardial images in 170 patients with exertional chest pain who were subsequently shown to have anatomically significant coronary artery disease.

Exercise ^{201}Tl myocardial images suggestive of ischaemia were seen in 126 patients (74%) compared with 111 (65%) who developed chest pain during exercise and 94 (55%) with electrocardiographic evidence of ischaemia. Patients with a history of atypical chest pain had a lower incidence of 'ischaemia' (54%) than patients with classical angina pectoris (80%). The demonstration of defects on exercise ^{201}Tl images increased with the extent and severity of the underlying coronary artery disease but was uninfluenced by the presence of previous myocardial infarction. Abnormal exercise ^{201}Tl images were seen in 110 of 144 patients (76%) achieving maximal symptom-limited exercise but in only 16 of 37 patients (43%) exercised to submaximal levels.

Exercise ^{201}Tl myocardial imaging is more sensitive than other exercise indices in the detection and assessment of coronary artery disease, but this is dependent on achieving maximal symptom-limited exercise. Simple quantification aids the interpretation of these images.

Exercise first-pass radionuclide ventriculography in patients with coronary artery disease

D. L. Stone, D. S. Dymond, A. T. Elliott, K. E. Britton, S. O. Banim, and R. A. J. Spurrell
St. Bartholomew's Hospital, London EC1A 7BE

Thirty-four patients with stable angina pectoris and coronary artery disease were studied by computerised first-pass radionuclide ventriculography at exercise-induced angina using a multicrystal gamma camera. Ejection fraction fell significantly ($P < 0{\cdot}0005$) from a mean of 61·1 rest to a mean of 52·9 on exercise. Extent of coronary artery disease was judged from coronary angiograms; a stenosis of greater than 50 per cent was regarded as significant. Ejection fraction fell significantly for the groups with triple vessel disease ($P < 0{\cdot}0005$) and with less extensive lesions ($P < 0{\cdot}05$). Fall in ejection fraction was significantly greater for those patients with triple vessel disease ($P < 0{\cdot}01$). All 5 patients with a fall in ejection fraction of greater than 15 per cent had triple vessel disease. There was no significant change in ejection fraction in a control group of normal patients. Wall motion abnormalities were assessed using a hemiaxial model. Thirty-four abnormal segments were induced by exercise; 10 anterior, 11 inferior, and 13 apical. All except 2 (1 inferior, 1 apical) were in regions supplied by significantly stenosed vessels. Exercise first-pass radionuclide ventriculography may be performed during angina to show changes in regional and general myocardial function. It is a useful screening test for coronary artery disease and may especially identify patients at high risk.

Editorial Notice

References

Contributors should note that, in future, references in the text of papers submitted to this journal and in the bibliography should be prepared in the new format, as outlined briefly in the Notice to contributors.

Full details of this new, uniform style, which was agreed at a meeting of the International Steering Committee of Medical Editors held in Vancouver, were published in the *Br Med J* (1979; **1**: 532–35) and *Ann Intern Med* (1979; **90**: 95–9). Reprints of this article are available from the *Br Med J* (price 50p).

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Cardiovascular epidemiology

International Joint Meeting on 'Cardiovascular Epidemiology', Crete, Greece, 9–10 September 1979. Organised by the Greek Society for the Study of Atherosclerosis and the seven-country heart study.

Inquiries: Professor Christ Aravanis, MD, 47 Queen Sophia Avenue, Athens, Greece.

Computers in cardiology

Sixth International Conference on 'Computers in Cardiology' will be held on 26–28 September 1979 in Geneva, Switzerland.

Information from: Computers in Cardiology, Centre de Cardiologie, Hôpital Cantonal, 1211 Geneva 4, Switzerland.

Past and present cardiology

Leiden University is organising an Einthoven meeting on 'Past and Present of Cardiology' under the sponsorship of the European Society of Cardiology on 1–2 November 1979.

Inquiries should be addressed to H. A. Snellen, MD, Department of Cardiology, University Hospital, Leiden, Netherlands.

Fifth annual pediatric echocardiography course

This course will be held on 15–19 October 1979 in Tel Aviv, Israel. It is sponsored by the American Society of Echocardiography and H.E.L.P.

Inquiries: Pediatric Echocardiography Course, 4340 Placita Panuco, Tucson, Arizona 85718, USA.

Fifth international symposium on atherosclerosis

Will be held on 6–9 November 1979 in Houston, Texas.

For information write: Dr A. M. Gotto, Chairman, Fifth International Symposium on Atherosclerosis, Baylor College of Medicine, The Methodist Hospital, 6516 Bertner Avenue, Houston, Texas 77030, USA.

World congress of angiology

This congress will be held in Athens, 7 to 12 September 1980. Particulars from Secretariat, XIIth World Congress of Angiology, 17 Sisini Str, Athens 612, Greece.

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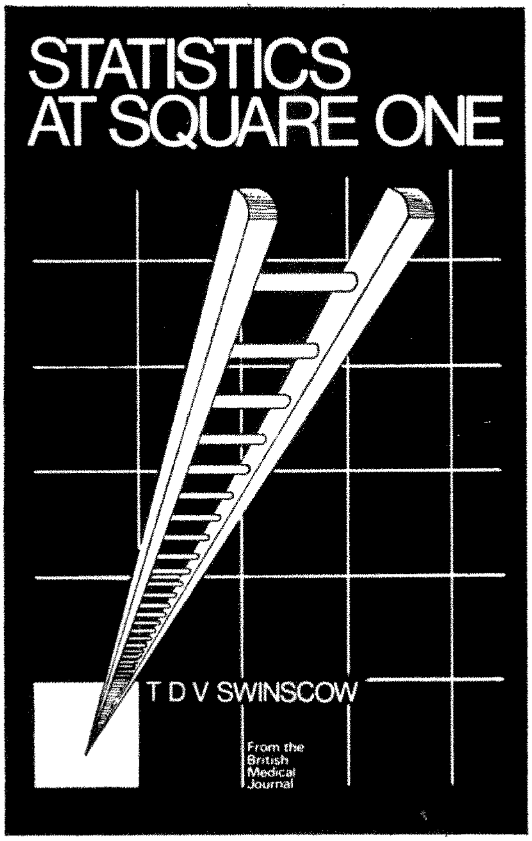

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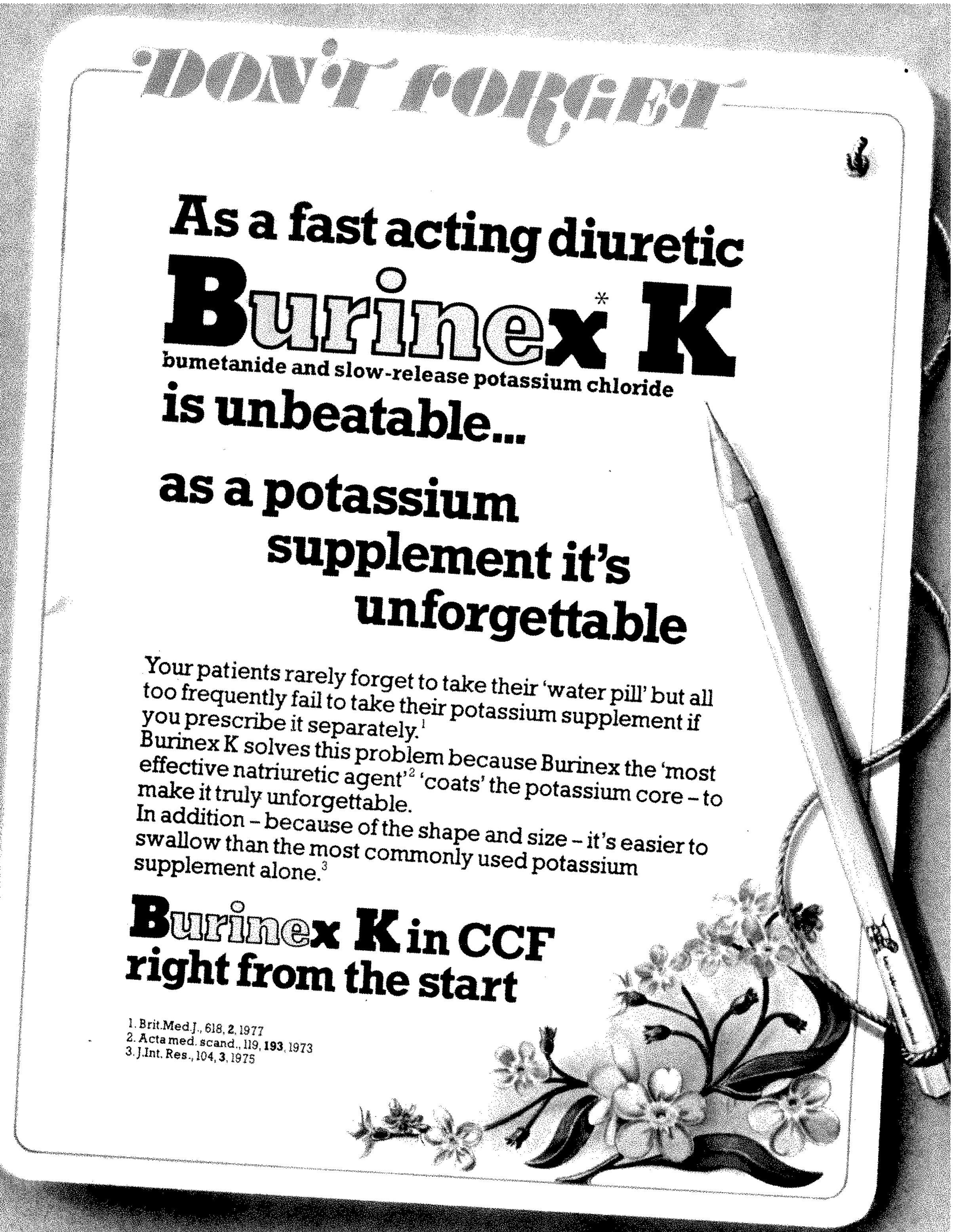

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   Walmsley R. Anatomy of left ventricular outflow tract. *Br Heart J* 1979;**41**:263–67.

(2) *Books and other monographs:*
   Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology 1977.* Edinburgh, London: Churchill Livingstone, 1978: 16–26.

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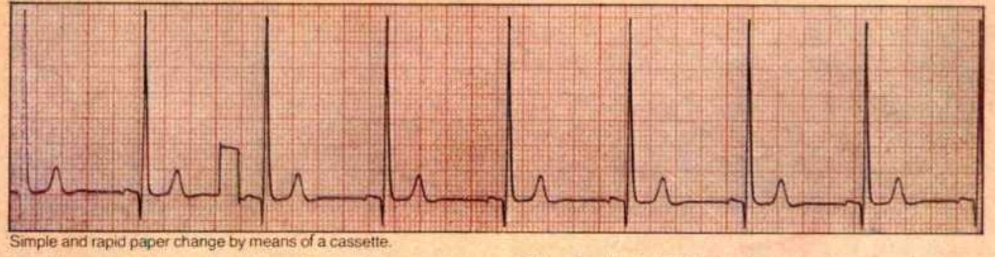

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Indications Treatment of hyperlipoproteinaemia, where full investigation has defined the abnormality, in conjunction with appropriate diet after diet alone has failed. Also indicated in: exudative diabetic retinopathy and in hyperlipoproteinaemia associated with diabetes; treatment of xanthomata associated with hyperlipoproteinaemia.

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6 U.S. expert committees have now reported on diet and heart disease.

6 recommend partial substitution of saturated fats by polyunsaturated fats.

1	Inter-Society Commission for Heart Disease Resources 1970. "Primary prevention of atherosclerotic diseases."	✓	4	American Medical Association Council on Foods and Nutrition 1972. "Diet and Coronary Heart Disease."	✓
2	American Health Foundation 1972. "Diet and Coronary Heart Disease."	✓	5	Select Committee on Nutrition and Human Needs 1977. "Dietary goals for the United States."	✓
3	White House Conference 1973. "Nutrition policies in the Seventies."	✓	6	American Heart Association Committee on Nutrition 1978. "Diet and Coronary Heart Disease."	✓

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"The proportion of saturated fatty acids in the diet be brought into proper balance.

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*American Heart Association 1978. "Diet and coronary heart disease." General dietary recommendations - Section 2.

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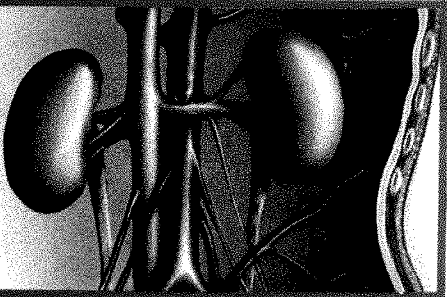

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Indications
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DOSAGE AND ADMINISTRATION
Initially 80 mg once daily. This dose may be increased by 80 mg increments at weekly intervals until an optimum response is obtained. Most patients respond to 240 mg or less, daily, but doses up to 640 mg have occasionally been used. In some patients it may be necessary to administer a diuretic, peripheral vasodilator and/or other anti-hypertensive agents in conjunction with nadolol in order to achieve satisfactory response. Dosage should be individually titrated.

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Like other drugs in this class, nadolol is contra-indicated in bronchial asthma; allergic rhinitis during the pollen season; sinus bradycardia and 2nd and 3rd degree heart block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure; during and within 2 weeks of administration of adrenergic augmenting psychotropic drugs such as monoamine oxidase inhibitors.

Warnings
Exacerbation of angina and myocardial infarction have occurred after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with angina pectoris or other evidence of coronary artery insufficiency.

The normal precautions associated with the use of beta-adrenergic blockers should be followed.

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta-adrenergic blocker should be gradual.

Nadolol should be used with caution in patients with impaired renal or hepatic function.

The safety of nadolol in pregnancy has not yet been established, and it should only be given to nursing mothers if deemed essential.

Side-effects
These resemble those reported with other beta-blocking drugs and rarely require withdrawal of treatment. They include gastro-intestinal effects, bradycardia, fatigue, light-headedness, cold extremities, insomnia, paraesthesia and dryness of the mouth. Cardiac insufficiency, hypotension and AV block have occurred on rare occasions. Overdosage or exaggerated response should be treated supportively and symptomatically.

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Presentation: Apresoline tablets each contain 25mg or 50mg hydralazine hydrochloride INN.

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Dosage: Initially 25mg (twice daily in combination with a beta-blocker plus thiazide diuretic e.g. Slow-Trasicor® and Navidrex®-K). This may be increased as necessary to a maximum dose of 200mg daily given in two or three divided doses.

Side effects: Tachycardia, headache, flushing, anorexia, nausea and vomiting can occur. All these side effects may be minimised by the prior administration of a beta-blocker.

Precautions: Occasionally patients on Apresoline develop rheumatic symptoms suggestive of rheumatoid arthritis. Also skin reactions and fever may occur, producing a syndrome similar to systemic lupus erythematosus. This is much more likely to occur with high doses and is rare if the maximum recommended dose of 200mg daily is not exceeded. If such symptoms should develop, the drug should be promptly discontinued, when remission will usually occur. Only rarely is it necessary to treat the reaction with corticosteroids. Apresoline should be used with caution in patients with coronary disease or undergoing anaesthesia (which may precipitate severe hypotension), or in patients taking tricyclic antidepressants or MAO inhibitors.

Contra-indications: Apresoline should be avoided in the first half of pregnancy. It should also be avoided in patients with tachycardia.

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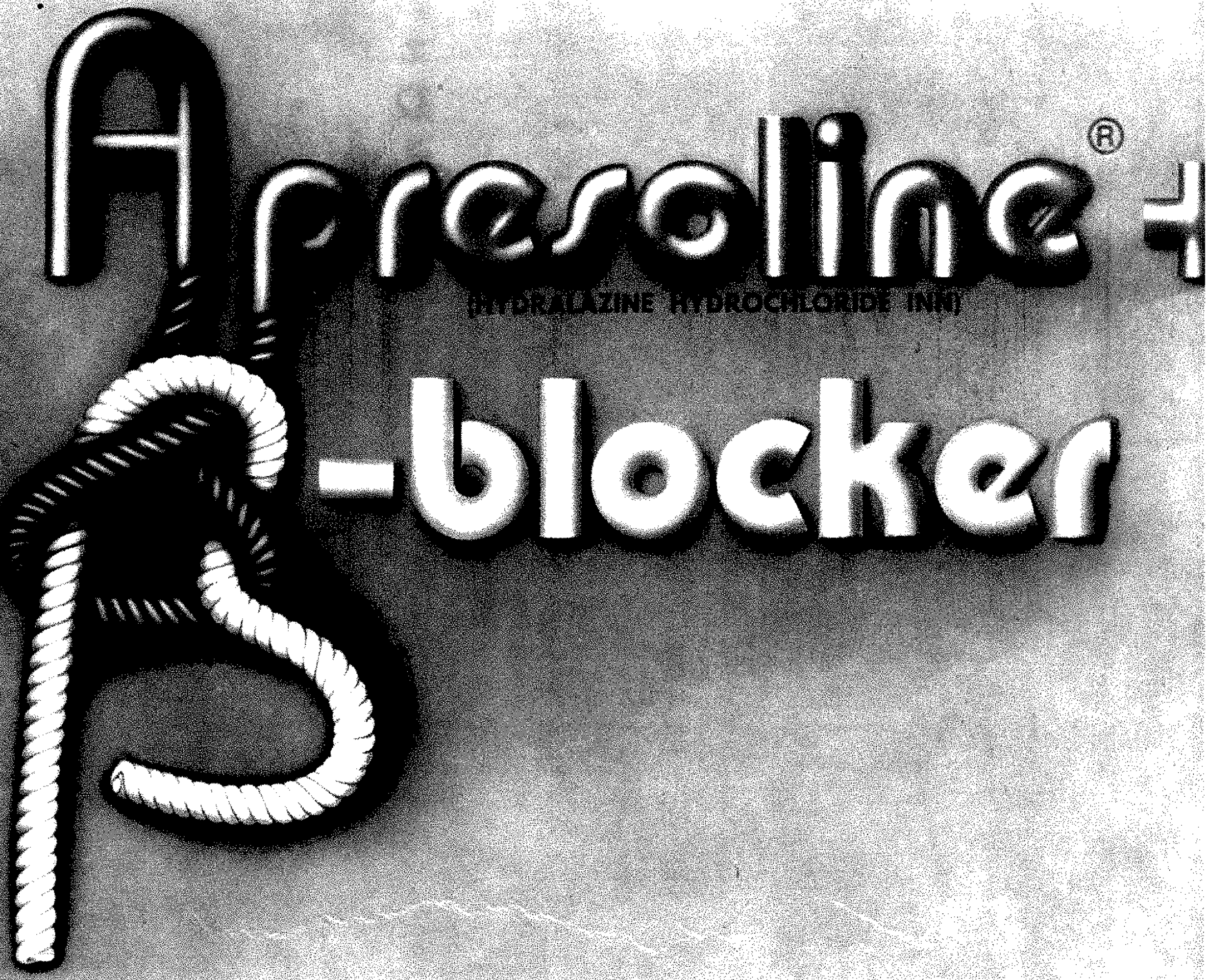

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Normal

Pericardial effusion.

Inferior Vena Cava entering right atrium.

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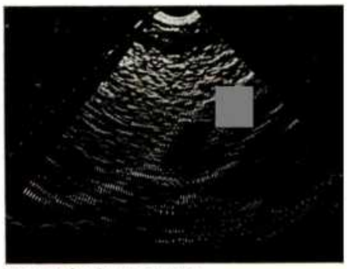
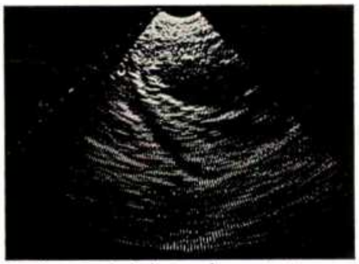


Tricuspid valve vegetation.



Small pericardial effusion, long axis view.

Pericardial effusion, short axis view.

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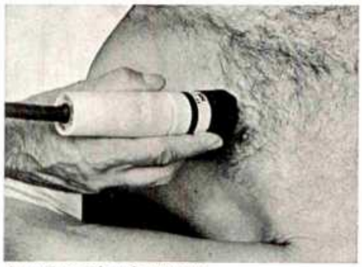

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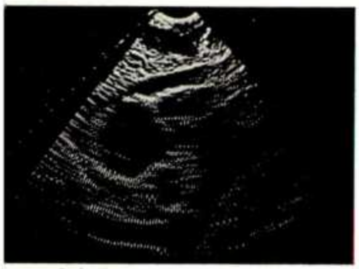

Pericardial effusion.

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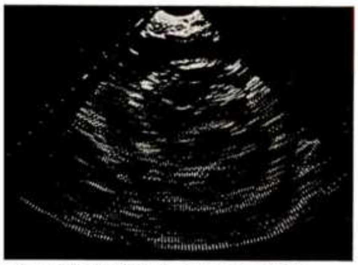

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Many authorities agree that elevated serum cholesterol is an important factor in the development of atherosclerosis. And, while it is not yet possible to assume that lowering cholesterol will reduce morbidity from coronary heart disease, most physicians accept the importance of maintaining serum cholesterol levels as close to normal as possible.

Colestid (colestipol), a new non-systemic agent developed by Upjohn research, effectively lowers serum cholesterol by an average 12–15% in Type II hyperlipidaemic patients – those with elevated cholesterol and normal or slightly elevated triglycerides.[1,2,3] A lowering of serum cholesterol by 19% has been demonstrated with 10 grams of Colestid given twice a day.

Colestid achieves a reduction in serum cholesterol by nterfering with the normal enterohepatic circulation of bile acids. Bile acids are synthesised in the liver from cholesterol and are secreted in bile into the intestine. Colestid works in the intestinal lumen, binding these bile acids and increasing the rate of their excretion. Less bile acid is available for reabsorption from the ntestine, and the liver must convert additional cholesterol to bile acid. The result is a reduction in plasma cholesterol levels.

Unlike other resin preparations, Colestid is well accepted by most patients. The odourless, tasteless granules may be mixed with a variety of liquids and oods, including fruit juices, milk, soups, pulpy fruits with a high water content, and carbonated beverages.

Colestid has produced no known interference with the action of coumarin anticoagulants, making it suitable for patients already under treatment for a heart condition. However, since Colestid may interfere with the absorption of certain drugs (e.g., chlorothiazide, tetracycline and penicillin G), the clinical response to concomitant medications should be closely monitored and appropriate adjustments made.

Most patients tolerate Colestid therapy very well. The most common side effect is mild constipation.

References: 1. Med. J. Aust. (1973). *1*:1223.
2. JAMA (1972). 222:676.
3. New Zealand J. Med. (1972). 76:12.

Prescribing Information

Presentations: Tasteless and odourless granules of colestipol hydrochloride. *Uses:* Adjunctive therapy to diet for treatment of hypercholesterolaemia, particularly Frederickson Type II. *Dosage and Administration:* Always mix with water or other fluids before ingesting. Oral total daily dosage for adult 15–30 grams. Take in divided doses 2–4 times daily. *Contraindications:* Hypersensitivity to colestipol. *Precautions, Warnings:* Not to be taken in dry form. Colestid may interfere with absorption of some drugs (e.g. penicillin G, tetracycline, chlorothiazide). Safety for use in pregnant women or children not established. *Package Quantities:* 30 x 5 g sachets; 250 g bottle. Each sachet or scoopful contains 5 g colestipol hydrochloride. *Further Information:* Colestid is not absorbed. It binds bile acids causing further cholesterol conversion to bile acids thus lowering serum cholesterol levels. *Basic NHS Costs:* 30 x 5 g sachets £8.90. 250 g bottle £13.76. Product Licence Nos. PL 0032/0055. PL 0032/0057. *Full Product information is available on request.*

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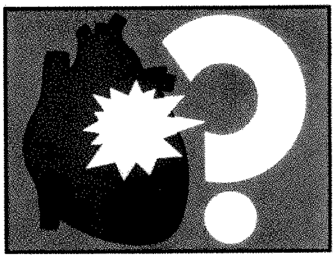

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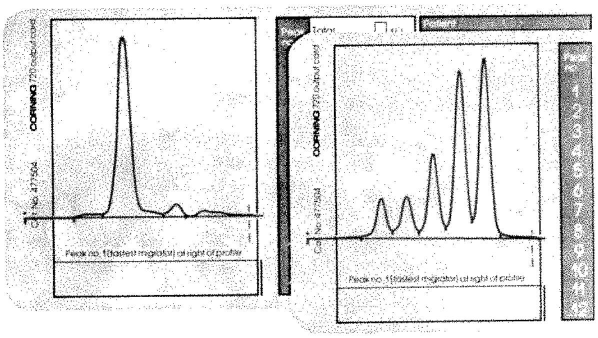

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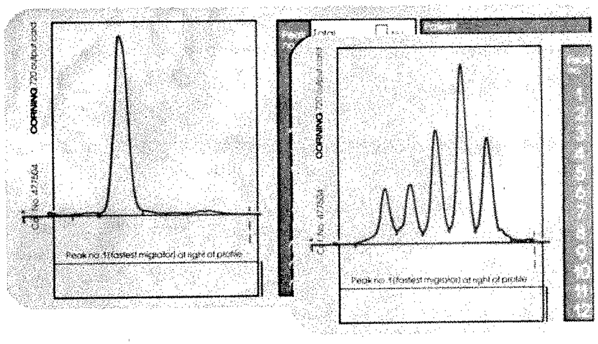

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Indications In the treatment of mild and moderate hypertension. The combination product may be suitable for use when satisfactory control of arterial blood pressure cannot be obtained with either a diuretic or a beta-blocking drug used alone.

Dosage *Adults:* One or two tablets once daily. Trasidrex can be combined with other antihypertensive drugs having a different pharmacological effect. In particular, a free combination with a vasodilator (e.g. Apresoline*) will often be beneficial.

Side effects Though mild gastro-intestinal upsets and dizziness may occur, especially at the start of treatment, they are rarely sufficiently severe to justify withdrawal of therapy. Drowsiness and insomnia occur infrequently. As with all beta-blockers bronchospasm, cold extremities, excess bradycardia and heart failure could be precipitated in susceptible patients.

Beta-blockers are occasionally associated with skin rashes and/or dry eyes. If any such reaction is suspected, treatment should be withdrawn gradually.

In common with other thiazides there have been reports of thrombocytopenia but these are rare. Thiazides can produce allergic skin reactions, mild anorexia and nausea and cause latent gout or latent diabetes to become manifest.

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Effect of glyceryl trinitrate on echocardiographic left ventricular dimensions during exercise in the upright position

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SUMMARY Changes in left ventricular size may be of importance in the development of angina and in its amelioration by glyceryl trinitrate, but left ventricular dimensions have not been measured during exercise in the upright position, the circumstance in which angina most often occurs. To assess changes in left ventricular end-systolic and end-diastolic dimensions, echocardiograms were obtained from 5 normal subjects and 6 patients with angina during rest and exercise upright, both before and after glyceryl trinitrate. The end-systolic dimension was considered an index of regional performance rather than an estimate of overall left ventricular behaviour. During exercise the end-diastolic dimension rose both in the normal subjects and in the patients. The end-systolic dimension fell progressively with exercise in the normal subjects but changed inconsistently in the patients. Glyceryl trinitrate lowered the end-diastolic dimension during exercise below comparable pretreatment values in both groups; the glyceryl trinitrate-induced decrease in end-diastolic dimension in the patients diminished at higher exercise levels. In all normal subjects and in 4 of the 6 patients with normal systolic shortening (= end-diastolic—end-systolic dimension) glyceryl trinitrate caused relatively small changes in the end-systolic dimension and systolic shortening on exercise. In contrast, in the 2 patients with hypokinetic ventricles glyceryl trinitrate conspicuously decreased the end-systolic dimension and increased systolic shortening.

Thus, during exercise, in the normal subjects and in the patients with normally functioning left ventricles on echocardiography, glyceryl trinitrate caused a modest fall in the end-diastolic dimension and little change in the end-systolic dimension, but in patients with ventricular hypokinesia it greatly improved regional contractile performance. Alleviation of ischaemic hypokinesia during exercise may be an important part of the benefit of glyceryl trinitrate.

Much is known about left ventricular dimensions during exercise supine (Sonnenblick *et al.*, 1965; Sharma *et al.*, 1976; Stein *et al.*, 1976; Borer *et al.*, 1978) but far less about the changes which occur when exercise is performed in an upright position. By favouring venous pooling within dependent portions of the body, the upright posture has been shown to cause a substantial reduction in left ventricular cavity dimensions in normal subjects at rest (DeMaria *et al.*, 1974; Redwood *et al.*, 1974). The extent to which this potential for venous pooling influences left ventricular dimensions during exercise when upright, however, has not been measured. Such postural influence may be particularly important when assessing the action of glyceryl trinitrate (GTN). Increased venous pooling is presumably a major factor causing decrease in left ventricular size when GTN is administered to resting upright subjects (DeMaria *et al.*, 1974; Redwood *et al.*, 1974) and though during exercise upright this mechanism is thought to play a significant part in the antianginal action of GTN, data documenting such an effect are lacking. Accordingly, echocardiographic measurements were made during exercise in the upright position both before and after glyceryl trinitrate in normal subjects and in patients with angina pectoris. Though echocardiographic results are not necessarily representative of dimensional changes in portions of the left ventricle not traversed by the ultrasound beam, particularly when systolic measurements are made

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in patients with coronary artery disease, data during systole may be useful in assessing changes in regional performance.

Methods

SUBJECTS

Technically satisfactory echocardiograms were obtained during exercise in 5 normal male subjects, aged 23 to 48 years, in whom the history, physical examination, electrocardiogram, and echocardiogram disclosed no evidence of cardiovascular disease. Four other normal subjects were excluded from the study because satisfactory echocardiograms could not be obtained during exercise.

Seven male patients, aged 36 to 61 years, had satisfactory echocardiograms during exercise. These subjects had been selected at random from an outpatient population with symptomatic coronary artery disease. Each had had typical stable angina pectoris for a varying duration (range 6 months to 12 years). Documented myocardial infarction (with persistent Q waves) had occurred several years previously in 2 patients. Electrocardiograms showed nonspecific T wave abnormalities at rest in 1 additional patient and significant ST segment depression during exercise in 2 others. Clinical examination showed no evidence of any other disease. No patient had an arrhythmia or overt congestive cardiac failure. Cardiac catheterisation was not performed in any subject. Four further patients with angina were excluded from the study because of technically unsatisfactory echocardiograms during exercise.

All subjects were fully acquainted with the purpose and procedures of the study and informed consent was obtained from each before participation.

STUDY PLAN

Echocardiograms were obtained at rest supine, at rest upright (subjects seated on a bicycle ergometer with their feet on the pedals), during the last 30 seconds of each 3-minute exercise level, and when a limiting symptom, such as angina appeared. Echocardiograms were recorded using an Aerotech Gamma transducer (2·25 MHz, 1·3 cm diameter, 10 cm focus) connected to an Ekoline 20 ultrasound unit. A Cambridge recorder (model 72112) transferred the resultant signal to light-sensitive paper moving at a speed of 50 mm/s. A conventional T-scanning technique was employed to ensure that measurements were made at a consistent site (Henry *et al.,* 1973). Satisfactory echocardiograms could usually be recorded during exercise on our upright bicycle ergometer (Godart) if subjects leaned forward. The operator held the transducer at the junction of the fourth or fifth intercostal space and the left sternal border, adjusting the transducer angle as necessary during exercise to maintain the desired image on a monitoring oscilloscope. In addition, an electrocardiographic lead (CM5) was monitored and systolic blood pressure was measured (using a pneumatic arm cuff) at rest and during exercise.

Normal subjects exercised for 3 minutes at each of 4 escalating work loads (40, 80, 120, and 160 Watts) without pausing. Using a procedure previously established (Redwood *et al.,* 1971) the work load for the patients with coronary disease, however, was increased by 20 Watts every 3 minutes, with the initial work load chosen individually so that angina developed in each subject when unprotected by GTN between the 4th and 7th minute of exercise, and this value was identified at practice sessions before the day of study. The work load at the point that angina occurred during the study (no GTN having been given) varied from 60 to 140 Watts, the patients' heart rates then ranging from 108 to 127 beats/min. Exercise was stopped (recordings having been obtained) within 30 seconds of the onset of pain. Unprotected by GTN all patients stopped exercise because of angina; after GTN 3 were halted at higher work loads by fatigue instead. All subjects showed normal rhythm and conduction throughout.

Studies were performed in the postabsorptive state. The 4 patients taking propranolol discontinued this drug at least 24 hours beforehand and no patient had had GTN for at least 12 hours. Each subject exercised first without drugs and then after a placebo sublingually. Finally, all normal subjects and 6 of the 7 patients exercised 3 minutes after sublingual GTN, 0·5 mg. Thirty minutes' rest supine was interposed between each period of exercise. (NB: Previous work (Redwood *et al.,* 1971) showed no change in exercise capacity in patients with angina during a third period of exercise unless such exercise was preceded by sublingual trinitrate administration.) The dose of GTN employed was sufficient to raise the heart rate at least 10 beats/min or lower the systolic blood pressure at least 10 mmHg in each subject when measurements were made at rest upright and it produced a rise in exercise capacity in each of the 6 patients with coronary disease (mean increase in duration of exercise = 3·8 min).

In 2 of the normal subjects, parts of the procedure were repeated on a subsequent day to evaluate the reproducibility of the measurements.

DATA ANALYSIS

Maximum and minimum values of the distance

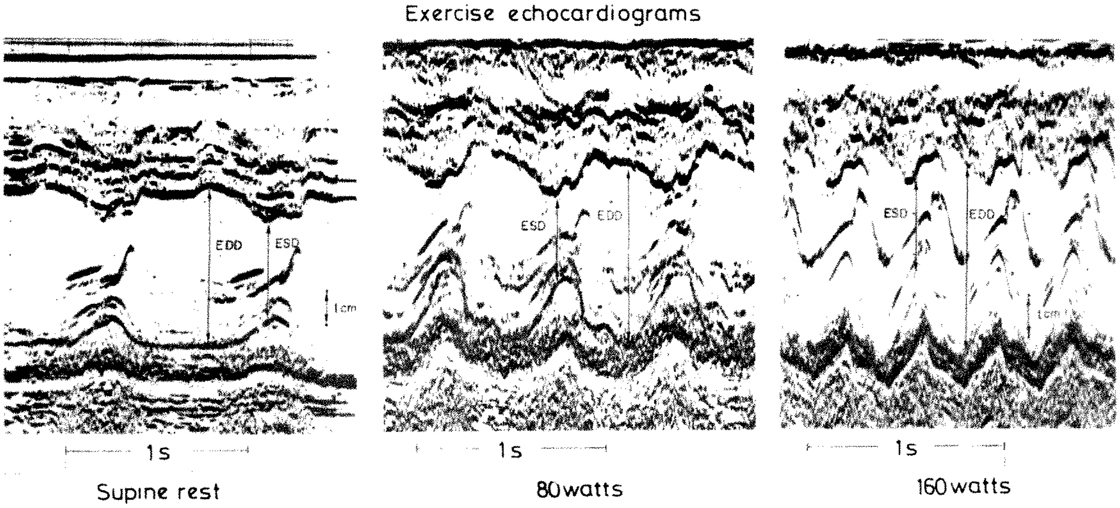

Fig. 1 *Echocardiograms are shown for one normal subject at rest supine* (left), *during moderate exercise* (centre), *and during strenuous exercise* (right) *on an upright bicycle ergometer. EDD, end-diastolic dimension; ESD, end-systolic dimension. Calibration markers, spaced 1 cm apart along a vertical axis, are identified in left and right panels.*

between left ventricular septal and free wall endocardial surfaces were taken to represent the left ventricular end-diastolic dimension (EDD) and end-systolic dimension (ESD), respectively (Fig. 1). Measurements were taken from the posterior border of the septal echo. The percentage shortening of left ventricular dimension was calculated as (1–ESD/EDD) × 100 per cent. Between 5 and 12 complexes (mean 8) were measured and the measurements averaged for each patient at each exercise level. Each resultant data point had a standard deviation averaging ±1·0 mm and a standard error averaging ±0·34 mm.

Paired comparisons were made using either two-tailed Student's t tests or a two-way analysis of variance.

Results

REPRODUCIBILITY

Measurements of left ventricular dimensions during comparable levels of exercise showed no significant alterations in 2 normal subjects studied on 2 different days. Mean changes in 16 determinations (±SD) comparing the first and second sets of results were −1·5 mm ± 3·2 for the end-diastolic dimension, 0·9 mm ± 2·4 for the end-systolic dimension, and 0·0 per cent ± 6·0 for percentage shortening. None of these differences is statistically significant. Similarly, the measurements made during exercise after placebo were indistinguishable from those obtained before it. In the 12 subjects studied mean changes (±SD) between the first and second periods of exercise were 0·5 mm ± 1·8 for the end-diastolic dimension, 0·2 mm ± 2·1 for the end-systolic dimension, and 0·0 per cent ± 3·5 for percentage shortening. None of these differences is statistically significant. Equally satisfactory reproducibility was observed in normal subjects and patients alike.

NORMAL SUBJECTS

The end-diastolic dimension decreased (mean 8·6%, $P < 0{\cdot}05$) when the upright posture was assumed (Fig. 2, left). The lowest level of exercise, 40 Watts, caused a rise in end-diastolic dimension in all 5 subjects (mean 8·7%, $P < 0{\cdot}01$) and this tended to reverse the fall associated with the upright posture. At higher exercise levels no consistent pattern was seen. Heart rates and systolic blood pressures before and during exercise are shown in the Table. There was no correlation with changes in end-diastolic dimension. The end-systolic dimension decreased uniformly (mean 14%, $P < 0{\cdot}01$) when supine subjects changed to the upright position (Fig. 2, centre) and decreased further progressively during the course of exercise. At maximal exercise levels the end-systolic dimension was, on average, 25 per cent below values at rest upright ($P < 0{\cdot}01$). Change from the supine to the upright position was associated with a small rise in percentage shortening (3%, $P < 0{\cdot}05$) (Fig. 2, right). In each subject, mean percentage shortening increased progressively with exercise from 41 per cent at rest upright to 59 per cent during maximal exercise ($P < 0{\cdot}01$).

The effect of GTN was assessed by examining differences between measurements made after this

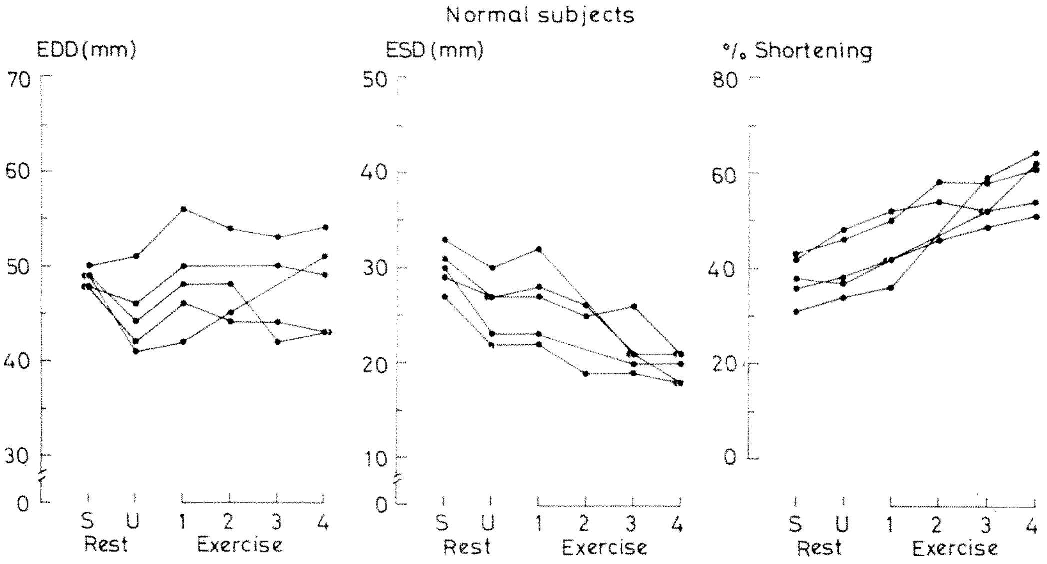

Fig. 2 *Values of end-diastolic dimension* (left), *end-systolic dimension* (centre), *and percentage systolic shortening (= (1-ESD/EDD) × 100 per cent, right) are shown as connected dots for each normal subject. S, rest supine; U, rest upright; exercise levels are numbered in order of their performance: 1, 40 Watts; 2, 80 Watts; 3, 120 Watts; and 4, 160 Watts.*

Table *Mean heart rate and blood pressure before and after GTN**

		Exercise levels			
	Rest upright	*40 Watts*	*80 Watts*	*120 Watts*	*160 Watts*
Normal subjects (n=5)					
Heart rate					
After placebo	77 ±3	100 ±3	114 ±6	135 ±8	156 ±5
After GTN	102 ±5	111 ±6	127 ±6	144 ±8	163 ±6
Systolic pressure					
After placebo	122 ±8	137 ±6	150 ±6	168 ±4	186 ±8
After GTN	106 ±5	122 ±6	137 ±11	151 ±8	161 ±7
Patients with angina (n=6)	*Rest upright*	*Level 1*	*Level 2*	*Level 3*	
Heart rate					
After placebo	79 ±2	113 ±4	124 ±4	—	
After GTN	90 ±2	113 ±4	125 ±4	136 ±4	
Systolic pressure					
After placebo	110 ±3	138 ±8	142 ±7	—	
After GTN	100 ±4	132 ±9	136 ±9	143 ±9	

* Mean values are shown ± standard error. Exercise levels for anginal patients are explained in text.
Abbreviations: GTN, glyceryl trinitrate.

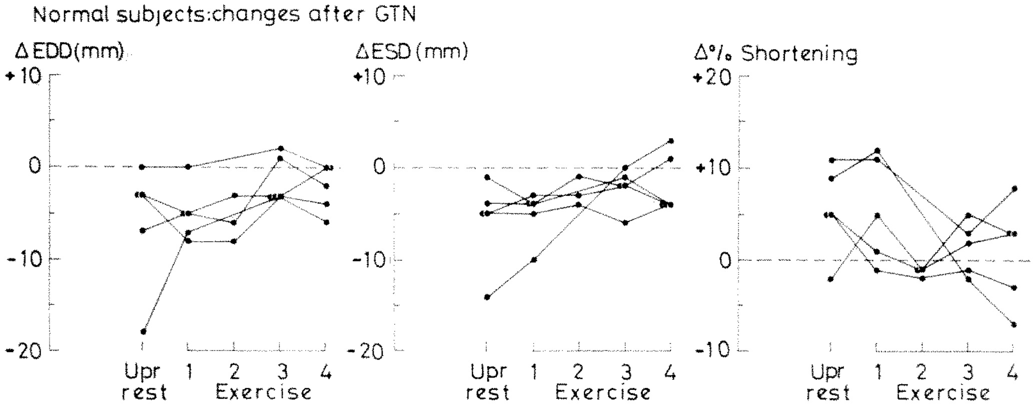

Fig. 3 *Changes in end-diastolic dimension* (left), *end-systolic dimension* (centre), *and percentage systolic shortening* (**right**) *after glyceryl trinitrate (GTN) are shown for each normal subject at rest upright (Upr) and during 4 levels of exercise. Displacement below the zero line (dashes) indicates decrease relative to comparable pre-GTN values.*

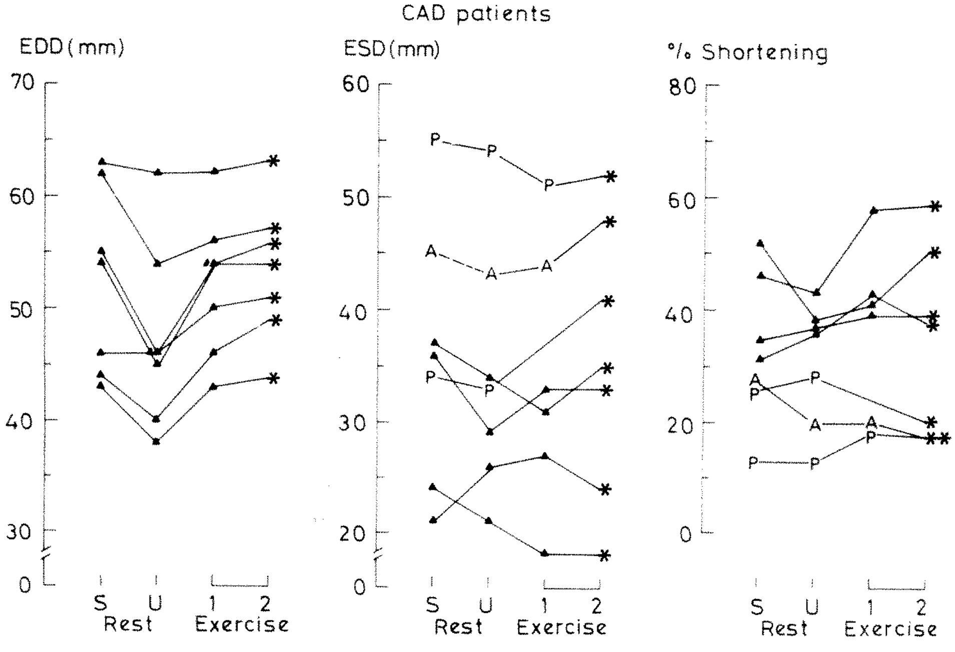

Fig. 4 *End diastolic dimension* (left), *end-systolic dimension* (centre), *and percentage systolic shortening* (right panel) *are shown as connected triangles or letters for each patient with angina. S, rest supine; U, rest upright; 1, subanginal exercise level (actual workload chosen individually for each patient); 2, exercise level (20 Watts more intense than level 1) associated with the onset of angina (asterisk) if exercise is not preceded by effective therapy; P, patients with posterior hypokinesia; A, patient with anterior hypokinesia. A point is omitted from the curve of one patient with posterior hypokinesia because satisfactory measurement of the end-systolic dimension could not be made from the echocardiogram obtained during level 1 exercise.*

drug and those made after placebo (Fig. 3). GTN reduced the end-diastolic dimension by a mean of 16 per cent ($P<0{\cdot}05$) in normal subjects at rest upright. The decrease in end-diastolic dimension persisted during the lower two levels of exercise (Fig. 3, left), but diminished at the higher two levels. Thus, the mean decrease was 5 mm or 10 per cent at 40 Watts ($P<0{\cdot}05$), but only 2·4 mm or 5 per cent (NS) at 160 Watts. The end-systolic dimension was consistently reduced after GTN by a mean of 5 mm or 19 per cent ($P<0{\cdot}02$) at 40 Watts, and 1·6 mm or 7 per cent (NS) at 160 Watts (Fig. 3, centre). GTN produced no consistent change in percentage shortening (Fig. 3, right). In no instance did percentage shortening after GTN increase by more than 8 per cent in normal subjects at exercise levels above 40 Watts.

Heart rates and systolic blood pressures during exercise after GTN are given in the Table.

PATIENTS WITH ANGINA

Patients showed a wider range of left ventricular dimensions than normal subjects; some had an abnormally large end-diastolic dimension (Fig. 4, left) and end-systolic dimension (Fig. 4, middle) when at rest supine. The end-diastolic dimension behaved much as it did in normal subjects: the decrease on the assumption of the upright position (mean 10%, $P<0{\cdot}01$) was almost always reversed completely at the lower level of exercise. A small but consistent additional increase in the end-diastolic dimension (mean 1·6 mm or 3·1%, $P<0{\cdot}05$) was noted at the higher level of exercise which produced angina. Unlike the normal subjects, the patients did not show a uniform fall in end-systolic dimension and rise in percentage shortening during exercise. On the contrary, end-systolic dimension remained unchanged or increased in 3 of 6 patients and percentage shortening remained virtually unchanged ($\pm 1\%$) or decreased during the higher exercise level in 5 of 6 patients. In a seventh patient end-systolic dimension could not be measured during the lower exercise level. Percentage shortening remained below 25 per cent throughout the course of exercise in 3 patients (Fig. 4, right). These individuals were considered to have distinctly hypokinetic segments within the region assessed by echocardiography. Percentage shortening actually decreased below resting values in 2 of these 3 patients; poor septal contraction was responsible in 1 and poor free wall contraction in the other 2.

The effect of GTN was assessed by examining the differences between measurements made after this drug and those made after placebo. When after

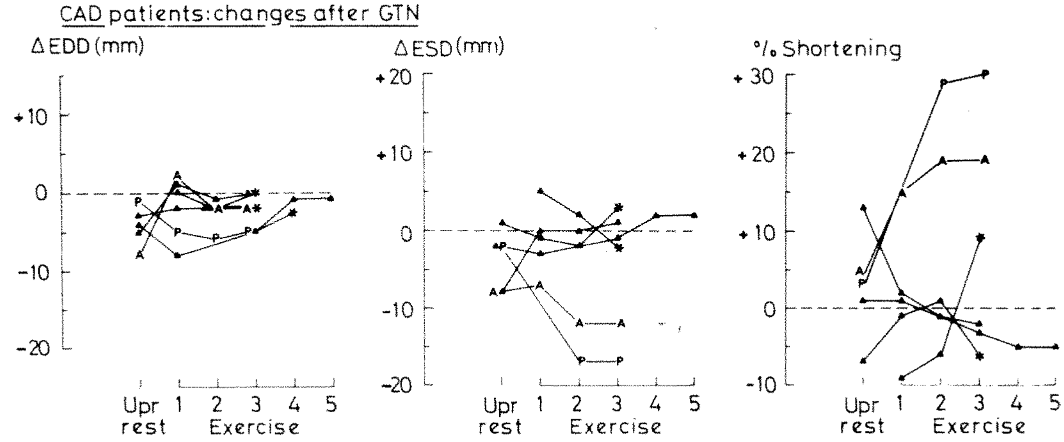

Fig. 5 *Changes in end-diastolic dimension* (left), *end-systolic dimension* (centre), *and percentage systolic shortening* (right) *after glyceryl trinitrate (GTN) are shown at rest upright (Upr) and during exercise. Each successive exercise level had a workload 20 Watts greater than the preceding level. Level 1 (same workload as level 1, Fig. 4) was chosen individually as described in text. Patients were able to reach levels 3 to 5 only after GTN. Thus, the value shown at each of these exercise levels represents the difference between measurement after GTN at levels 3, 4, or 5, and the measurement made for the same patient during maximal exercise before GTN (level 2). Termination of* post-*GTN exercise by angina is denoted by an asterisk; lines ending without an asterisk indicate post-GTN limitation by fatigue. Post-GTN systolic function during exercise was much improved in patients with posterior (P) or anterior (A) hypokinesia during pre-GTN exercise. Nevertheless, one of these patients (A) showed very little change in end-diastolic dimension during post-GTN exercise. Two points are omitted from one curve and one point from a second curve in the centre and right panels where the end-systolic dimension could not be measured satisfactorily.*

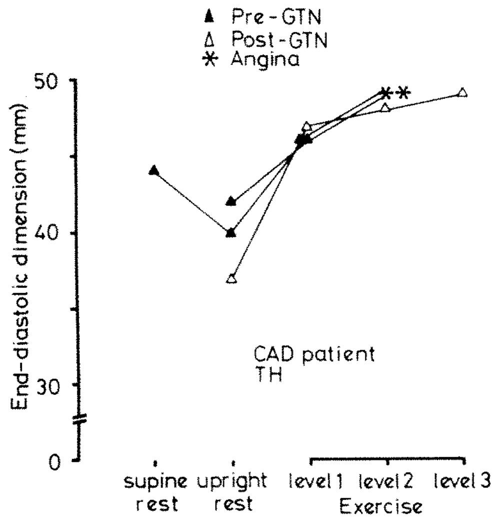

Fig. 6 *End-diastolic dimension for one particular patient with angina (T. H.) is shown at rest and during exercise at 100 Watts (level 1) and 120 Watts (level 2) before* (closed triangles) *and after* (open triangles) *glyceryl trinitrate (GTN) and at 140 Watts (level 3) after GTN. Results during the first exercise level (no prior therapy) are joined to a preceding measurement at rest supine. The second exercise level (post-placebo) yielded very similar values to the first and, like the first, ended with onset of angina* (asterisk). *The third exercise level (post-GTN) showed a 3-mm reduction in the end-diastolic dimension at rest upright but no reduction greater than 1 mm during any of the exercise levels. Nevertheless, angina did not appear after GTN, even at a workload 20 Watts greater and at an end-diastolic dimension equal to that at the onset of angina before GTN.*

GTN, patients were able to exercise at levels not reached after placebo, measurements at the highest level attained in each case were used for purposes of comparison.

At rest upright the end-diastolic dimension was uniformly decreased (mean 10%, $P<0{\cdot}01$) after GTN (Fig. 5, left). Those 2 patients able to exercise longest after GTN showed persistent substantial ($\geqslant 5$ mm) GTN-induced decrement in end-diastolic dimension during most of their exercise. In 3 other patients, however, the GTN-induced decrease in end-diastolic dimension seen at upright rest dwindled to $\leqslant 2$ mm (4%) or disappeared entirely during the first or second exercise level. In a fourth patient with no rest measurement, GTN-induced decrease in end-diastolic dimension remained small ($\leqslant 2$ mm) throughout the course of exercise. Thus, the beneficial effects of GTN were sometimes, not always, accompanied by a substantial decrease in the end-diastolic dimension during exercise. There was no difference in heart rate or systolic pressure distinguishing individuals with substantial GTN-induced decrements in end-diastolic dimension at higher levels of exercise from others who did not show this.

GTN-induced changes in end-systolic dimension and percentage shortening (Fig. 5, middle and right) were even less uniform. In the 4 patients with relatively good systolic function on the echocardiogram, GTN effects were minor and inconsistent, but in 2 of the 3 in whom the ultrasound beam showed severe hypokinesia GTN caused a pronounced, sustained decrease in the end-systolic dimension (maximum 12 and 17 mm) and a very large increase in percentage shortening (maximum 19 and 30%). The third patient with hypokinesia was not studied after GTN. Thus, GTN improved systolic function during exercise in hypokinetic regions of the left ventricle but had no consistent effect on the ventricles of normal subjects, or on those of patients in whom myocardial contraction on echocardiography had been shown to be relatively normal beforehand.

Heart rates and systolic blood pressures in this group are also given in the Table.

Discussion

Our findings indicate that satisfactorily reproducible values for the echocardiographic left ventricular end-diastolic and end-systolic dimensions can be obtained during bicycle exercise in the upright position. In the homogeneously contracting hearts of normal subjects it is likely that changes in left ventricular cavity dimensions along the single axis defined by the ultrasound beam are qualitatively (if not quantitatively) similar to changes occurring elsewhere within the left ventricle. Such similarity is unlikely in the less homogeneous contraction often seen in the ventricles of patients with coronary disease, particularly during systole, but even in this group changes in left ventricular cavity dimensions may be valuable in assessing local responses to physiological or pharmacological influences.

LEFT VENTRICULAR DIMENSIONS IN NORMAL SUBJECTS

Left ventricular end-diastolic and end-systolic dimensions decreased, and percentage shortening rose slightly when the supine normal subjects assumed the upright position (Fig. 2), findings that are in agreement with a previous study on the effect of postural change on echocardiographic dimensions (Redwood *et al.,* 1974). Reversal of the decrease in the end-diastolic dimension occurred at the lowest level of exercise, probably because of mobilisation of blood pooled in dependent portions of the body by the pumping action of exercising muscles and increased respiration, and by increased sympathetic venoconstrictor activity (Bevegård and Shepherd, 1965, Freyschuss, 1970), but little further change was noted in most subjects during much more strenuous effort. Stein *et al.* (1976) reported similar findings in supine subjects. Thus, under ordinary physiological conditions the left ventricular end-diastolic dimension does not appear to increase beyond the value observed at rest when supine. However, progressively more strenuous exercise in the upright position produced correspondingly progressive decreases in the end-systolic dimension and rises in percentage shortening. These data are consistent with evidence from radionuclide cineangiography that the ejection fraction rises progressively in supine normal subjects when they perform increasingly strenuous exercise (Borer *et al.*, 1977). Though caution must be used in accepting our data as representative of dimensional changes occurring throughout the left ventricle, they suggest that when upright normal subjects perform exercise, the concomitant rise in left ventricular output is produced primarily by increases in heart rate and in systolic emptying with little change in left ventricular end-diastolic volume.

GTN decreased the end-diastolic and end-systolic dimensions below corresponding placebo values at rest when upright (Fig. 3), reflecting, in part, the tendency of this drug to exaggerate venous pooling in the upright position. The size of these changes caused by GTN in our seated subjects corresponds more closely to those seen in subjects at 30° head-up tilt (DeMaria *et al.*, 1974; Redwood *et al.*, 1974) than to those in supine subjects (Williams *et al.*, 1965; Burggraf and Parker, 1974; DeMaria *et al.*, 1974). GTN-induced decreases in left ventricular dimensions diminished substantially during exercise, however, particularly during the higher workloads. It is unlikely that this effect is attributable to diminishing activity of the drug since it is pharmacologically active for at least 15 minutes after sublingual administration (Goldstein *et al.*, 1971). More probably, mechanisms reducing venous pooling during exercise in the upright position in the absence of drugs reduce the tendency to venous pooling initiated by GTN. Regardless of the exact mechanisms involved, our data indicate that the GTN-induced decrease in the left ventricular end-diastolic dimension observed at rest (Williams *et al.*, 1965; Burggraf and Parker, 1974; DeMaria *et al.*, 1974; Redwood *et al.*, 1974) cannot be assumed to remain unaltered during exercise upright.

LEFT VENTRICULAR DIMENSIONS IN ANGINAL PATIENTS

Unlike the normal subjects, the patients with angina, as a group, showed a diversity in left ventricular dimensions at rest that probably reflected differences in the degree of disordered contraction of the region of myocardium traversed by ultrasound beam as well as differences in overall left ventricular performance (Fig. 4). Nevertheless, the pattern of response of the end-diastolic dimension in them was very similar to that of the normal subjects, a mean 9 per cent reduction in the end-diastolic dimension upon assuming the upright position being reversed at the lower level of exercise. The end-diastolic dimension again increased slightly at the higher level of exercise and, notably, at this point, just after the onset of angina, differed very little from the value during exercise before angina. In our study (all ambulatory patients) the production of angina by exercise in the upright position was never accompanied by a large abrupt expansion of left ventricular end-diastolic size. The effects of ischaemia were more clearly evident in the absence in nearly all of them of the normal decrease in the end-systolic dimension and rise in percentage shortening. This is consistent with the failure of the ejection fraction, measured by radionuclide cineangiography, to rise normally in patients with coronary disease performing exercise supine (Borer *et al.*, 1977).

GTN, in doses producing a lowered blood pressure or an increased heart rate and a raised exercise capacity in every patient, caused changes in the end-diastolic dimension (Fig. 5, left) closely resembling those noted in the normal subjects. Thus, at rest in the upright position the end-diastolic dimension was substantially decreased relative to resting values after placebo. As in normal subjects, the decrease was less at higher exercise levels; the majority of patients showed very little decrease in end-diastolic dimension while exercising at intensities in excess of those necessary to produce angina in the absence of GTN. One such individual (Fig. 6) showed that a substantial increase in exercise capacity could occur with virtually no GTN-induced reduction in the simultaneously measured end-diastolic dimension. Thus, though certain patients during exercise after GTN have such a decrease, this is not invariable even when angina is prevented.

In most of the patients GTN had the same small and inconsistent effect on the end-systolic dimension and on percentage shortening as it had in the normal subjects. In two, both with relatively severe hypokinesia present on echocardiograms before GTN, however, the drug produced a large decrease in the end-systolic dimension and increase in percentage shortening during exercise. This finding must be regarded as inconclusive because of the small number but is consistent with the GTN-induced improvement in systolic function in hypokinetic segments recently shown by radionuclide cineangiography during exercise supine (Borer *et al.*, 1978), and with earlier similar observations made at supine rest by contrast angiography (Helfant *et al.*, 1974; Sniderman *et al.*, 1974; McAnulty *et al.*, 1975). The mechanism may be the alleviation of regional myocardial ischaemia resulting from a reduction in myocardial oxygen consumption, or an increase in coronary collateral flow to potentially ischaemic areas or, lastly, a reduction in left ventricular afterload having a disproportionately beneficial action on myocardium weakened by ischaemia (Theroux *et al.*, 1976). Indeed, all three occur. It is worthy of note that improvement in systolic function was not always associated with a substantial reduction in the simultaneously measured end-diastolic dimension (Fig. 5, left) even when this was measured at the site of such improvement. Thus, neither objective benefit (the relief of systolic hypokinesia during exercise), nor subjective benefit (the prevention of angina) was consistently associated with a decrease in left ventricular end-diastolic dimensions.

IMPLICATIONS RELATING TO ANTIANGINAL EFFICACY OF GLYCERYL TRINITRATE

Our data have important implications in relation to possible mechanisms of GTN-induced relief of exertional angina in patients with chronic coronary occlusive disease. GTN has been thoughout to act, at least in part, by decreasing left ventricular dimensions during exercise. By diminishing the principal radii of curvature for each portion of the left ventricle (Burton, 1962), GTN could reduce left ventricular wall stress through the Laplace relation. Reduced wall stress during the first third of systole would lower myocardial oxygen consumption (Monroe, 1964) and thereby improve the balance of oxygen demand and supply. Reduced wall stress during diastole might also facilitate coronary blood flow to ischaemic areas by diminishing stretching forces on collateral vessels and capillaries. The Laplace relation, however, implies that wall stress would be reduced only in proportion to the decrease in left ventricular linear dimensions (such as the end-diastolic or end-systolic dimension) and not in proportion to the (much larger) associated decrease in left ventricular volume. Similar conclusions may be derived from calculations directly relating circumferential wall stress and left ventricular echocardiographic dimensions (Ratshin *et al.*, 1974).

Our results favour the hypothesis postulating GTN-induced reduction in wall stress during exercise in the upright position in that the left ventricular end-diastolic dimension decreased to some degree in all 6 patients and substantially (over 10%) for long periods in 2 of them.

In the other 4 patients, however, the observed decreases were very small (under 4%). One patient (Fig. 6) had no measurable decrease during the time when, protected by GTN, he was not only free of angina but also exercising at a greater intensity than his previous maximum. It is possible that a very small decrease in left ventricular wall stress may lead to a disproportionately large fall in myocardial oxygen consumption but there is no experimental verification for this. Our data do not suggest that a decrease in left ventricular cavity size during early systole is an important mechanism by which GTN prevents or forestalls angina during exercise upright.

Although GTN-induced reductions in the end-diastolic dimension during exercise were small, associated decreases in left ventricular diastolic pressure during exercise may have been substantial (Parker *et al.*, 1966). By decompressing collateral vessels and the capillaries within potentially ischaemic tissue, such decreases can significantly augment coronary collateral blood flow (Kjekshus, 1973). This influence, and the oxygen-sparing effect of a reduction in left ventricular systolic pressure, may be the most important benefits conferred by GTN, but our results suggest that, in certain patients, relief of localised systolic hypokinesia may also have a role. In addition to improving left ventricular systolic function, relief of hypokinesia might, in itself, exert a favourable influence by reducing local systolic wall stress, thereby reducing myocardial oxygen consumption specifically within potentially ischaemic portions of the left ventricle.

We wish to thank Dr Brian F. Robinson and Dr Aubrey Leatham of St. George's Hospital for their advice and encouragement.

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M-mode and cross-sectional echocardiographic study of the left ventricular wall motions in complete left bundle-branch block

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SUMMARY M-mode and cross-sectional echocardiograms of 37 patients with complete left bundle-branch block were compared with those of 5 patients with complete atrioventricular block during right ventricular pacing, 20 patients with anteroseptal infarction, and 20 normal subjects.

Of 37 patients with complete left bundle-branch block, 35 showed 3 types (A, B, and C) of abnormal septal motion and 2 patients showed normal septal motion. In type A and B, early and abrupt posteriorly-directed motion of the septum occurred during the pre-ejection period. After this early abnormal motion, the septum moved anteriorly in type A and posteriorly in type B. Type C exhibited akinetic or dyskinetic septal motion throughout systole. The onset of posterior wall contraction was delayed in all patients with complete left bundle-branch block.

These patterns of abnormal septal motion were observed in almost all portions of upper- to mid-septum that could be recorded by cross-sectional echocardiography.

Abnormal septal motion of types A and B was also observed during right ventricular pacing. It is suggested that abnormal septal motion of types A and B could be explained by asynchronous contraction of the left ventricle, with delayed activation of the left side of the septum and of the left ventricular free wall.

The septal motion of type C is almost the same as that seen in patients with extensive septal infarction. Most of the patients having abnormal septal motion of type C had electrocardiographic and vectorcardiographic findings which were compatible with extensive septal infarction. Thus patients with complete left bundle-branch block and type C motion may have sufficient septal damage to prevent the early posterior motion seen in type A and B patients. Different sequence of ventricular activation will be responsible for the difference between type A and B. It is also possible that some patients with type A septal motion may have septal damage to some degree, in contrast to type B.

Normal septal motion recorded in 2 patients with complete left bundle-branch block might be the result of a peripheral block of the left bundle-branch.

M-mode and cross-sectional echocardiography have proved to be valuable in the study of left ventricular wall motion and the assessment of left ventricular function (Diamond *et al.*, 1971; Jacobs *et al.*, 1973; Fujii *et al.*, 1976).

Recently, echocardiography has disclosed a characteristic ventricular septal motion in patients with left bundle-branch block (McDonald, 1973; Dillon *et al.*, 1974). It has been suggested that abnormal septal motion is related to an altered sequence of activation and contraction. However, no studies have been performed to analyse the left ventricular wall motion in left bundle-branch block by cross-sectional echocardiography.

The purpose of this study was (1) to analyse the motion of the interventricular septum and the left ventricular posterior wall in patients with complete left bundle-branch block by M-mode and cross-sectional echocardiography; (2) to relate septal motion during right ventricular endocardial pacing to that in complete left bundle-branch block; and (3) to compare septal motion in complete left bundle-branch block with that in septal infarction.

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Materials and methods

M-mode and cross-sectional echocardiograms of 37 patients with complete left bundle-branch block were compared with those of 5 patients with complete atrioventricular block during right ventricular endocardial pacing, and 20 patients with anteroseptal infarction without complete left bundle-branch block. All 62 patients had normal sinus rhythm. There were 41 men and 21 women. The mean age was 63 years (range 40 to 76). Complete left bundle-branch block was defined according to Massie and Walsh (1960). All 37 patients with complete left bundle-branch block had a QRS duration of 0·12 second or wider (mean 0·135 second). Basic disorders of patients with complete left bundle-branch block are old myocardial infarction (11 patients), angina pectoris (4 patients), congestive cardiomyopathy (6 patients), aortic valve disease (3 patients), hypertrophic cardiomyopathy (2 patients), hypertension (2 patients), and unknown (9 patients). The diagnosis of myocardial infarction was made on the basis of clinical history, increased serum enzyme activity, and electrocardiographic findings. All 5 patients with complete atrioventricular block of unknown aetiology showed normal septal motion before pacing. One of them had left ventricular anterior wall pacing after right ventricular endocardial pacing because of pacing failure. Twenty normal subjects were used as controls.

M-mode and cross-sectional echocardiograms were recorded simultaneously with the electrocardiogram and phonocardiogram, using ALOKA SSD-33 and SSD-110 instruments with a 2·25 MHz unfocused transducer of 10 mm diameter at a repetition rate of 1000 impulses per second (Fujii *et al.*, 1976). Ultrasonic cross-section B-scans were made along the long axis of the left ventricle, with the transducer tilting in sector arc from the base of the heart to the apex, at end-diastole (the onset of R wave in the electrocardiogram), early systole (D point, shown in Fig. 2), and end-systole (aortic component of the second heart sound in phonocardiogram), respectively (Fujii *et al.*, 1976).

Results

The interventricular septum moves slightly in an anterior direction during isovolumetric contraction and shows major posterior motion during subsequent ventricular ejection. In early diastole, it moves anteriorly and returns gradually to a more anterior position during diastasis. Septal motion is of smaller amplitude than posterior wall motion and moves in the opposite direction to posterior wall motion throughout almost the entire cardiac cycle except end-systole. Synergic motion is also shown in the whole extent of the left ventricular wall by cross-sectional echocardiography (Fig. 1).

Of 37 patients with complete left bundle-branch

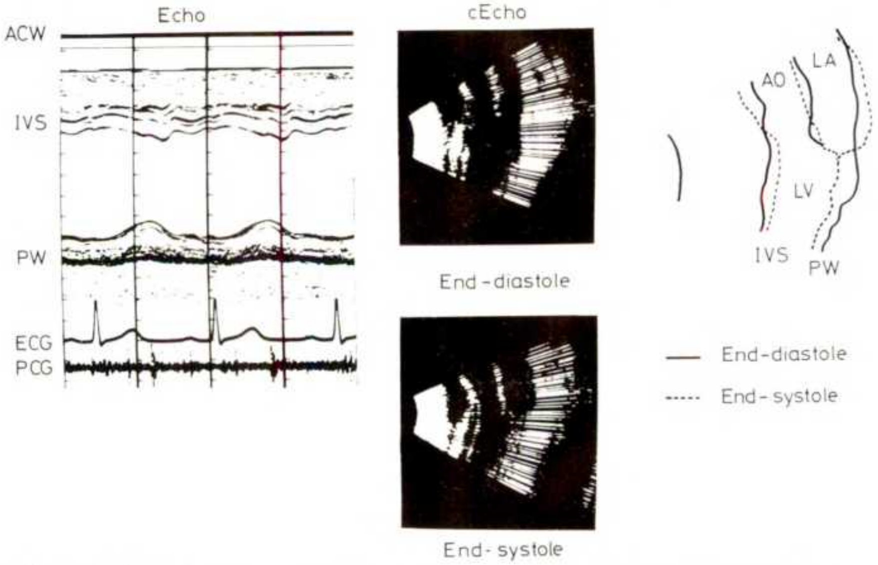


Fig. 1 *Echocardiogram (Echo) and cross-sectional echocardiogram (cEcho) through the long axis of the left ventricle at end-diastole and end-systole in a normal subject.*
ACW, anterior chest wall; IVS, interventricular septum; PW, posterior wall; LA, left atrium; LV, left ventricle; AO, aorta.

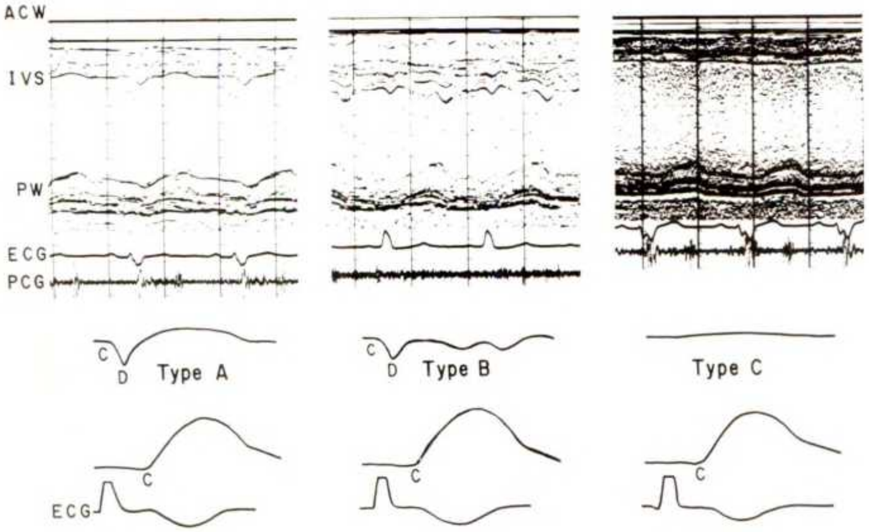


Fig. 2 *Echocardiograms showing 3 types (A, B, C) of abnormal septal motions in patients with complete left bundle-branch block.*

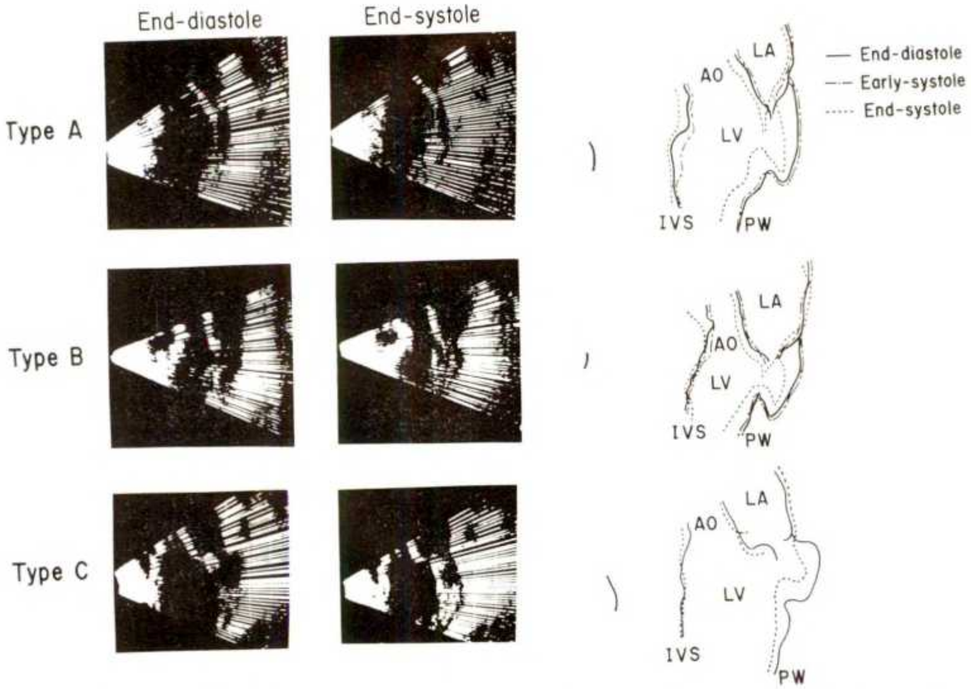


Fig. 3 *Cross-sectional echocardiograms through the long axis of the left ventricle at end-diastole, early systole, and end-systole in patients with complete left bundle-branch block, who showed abnormal septal motions of types A, B, C.*

block, 35 were found to have 3 types (A, B, C) of abnormal septal motion while the other 2 patients had normal septal motion (Fig. 2).

Among the 35 patients with abnormal septal motion, 23 showed early and abrupt posterior-directed motion of the septum occurring within 51 ± 23 ms (mean ± 1 SD) of the onset of the QRS. The amplitude of this motion was 4 ± 1 mm. After this early abnormal motion, the septum moved anteriorly in 10 patients (type A) and posteriorly in 13 patients (type B); 12 patients exhibited akinetic or dyskinetic septal motion throughout systole without early systolic abnormal motion (type C). Akinetic or dyskinetic septal motion with early systolic posterior motion of small amplitude (less than 2 mm) was included in type C.

The onset of posterior wall contraction occurred within 152 ± 30 ms after the onset of the QRS in all patients with complete left bundle-branch block. This is significantly delayed ($P < 0{\cdot}01$) since the mean value for normal subjects is 93 ± 14 ms. Cross-sectional echocardiography revealed that the abnormal septal motion occurred in upper- to mid-portions of the septum which could be recorded (Fig. 3).

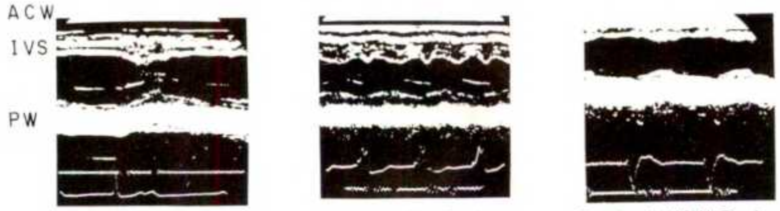
The abnormal septal motion of types A and B were also observed during right ventricular endocardial pacing in patients with complete atrioventricular block (Fig. 4). Patients with the pacing catheter-tip in the mid-portion of the right ventricle showed abnormal septal motion of type A. With right ventricular apical pacing, abnormal septal motion of either type A or type B occurred. One patient with abnormal septal motion of type B during right ventricular endocardial pacing showed almost normal septal motion during epicardial pacing of the left ventricular anterior wall (Fig. 4).

Septal motion of type C detected by M-mode and cross-sectional echocardiography was similar to that seen in patients with anteroseptal infarction (Fig. 5). All the 12 patients with type C septal motion had documented cardiac diseases which consisted of either myocardial infarction or congestive cardiomyopathy.

Electrocardiographic and vectorcardiographic ab-

Table *Relation between types of abnormal septal motion and abnormal electrocardiographic and vectorcardiographic findings*

	Electrocardiogam			*Vectorcardiogram*		
		Abnormal Q in I, aVL, V5, 6, or V1–3			*Initial vector directed right-anteriorly or left-posteriorly*	
Type of septal motion	*No. of patients*	(+)	(−)	*No. of patients*	(+)	(−)
A	10	2	8	9	3	6
B	13	2	11	13	3	10
C	12	9	3	9	8	1
Normal	2	1	1	1	0	1
n	37	14	23	32	14	18



Before Pacing During RV Pacing During LVAW Pacing

Fig. 4 *Echocardiograms before and during right ventricular (RV) pacing and the epicardial pacing of the left ventricular anterior wall (LVAW) in a patient with complete AV block. Echocardiograms before pacing and during LVAW pacing showed almost normal septal motion and that during RV pacing showed abnormal septal motion of type B.*

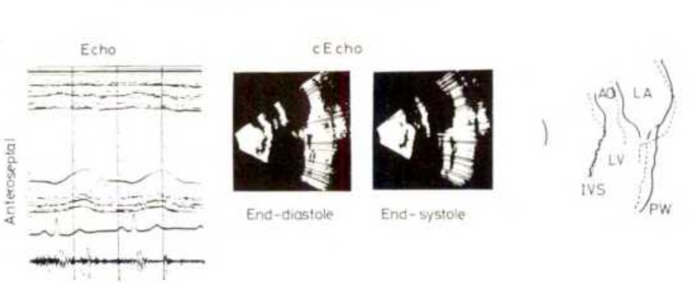


Fig. 5 *Echocardiogram and cross-sectional echocardiograms through the long axis of the left ventricle at end-diastole and end-systole in a patient with anteroseptal infarction. Septal motion is dyskinetic, similar to abnormal septal motion in type C.*

normalities, which were consistent with extensive septal infarction with complete left bundle-branch block (Chapman and Pearce, 1957; Scott, 1962; Doucet *et al.,* 1966), were observed in 75 per cent and 89 per cent of patients with abnormal septal motion of type C, respectively, contrasting with type A (20%, 33%), and type B (15%, 23%) (Table). These abnormal findings consisted of abnormal Q waves in leads I, aVL, or anterior chest leads, with complete left bundle-branch block. Vectorcardiographic abnormalities consisted of an initial vector directed rightward and anteriorly or leftward and posteriorly.

Discussion

Systolic contraction of the normal human left ventricle is a symmetrical and orderly process which depends on the normal rapid spread of myocardial activation (Amer *et al.,* 1960; Durrer *et al.,* 1970; McDonald *et al.,* 1972). The present study showed that patients with complete left bundle-branch block have 3 types of abnormal septal motion, in contrast to normal subjects. These abnormal septal movements were observed in almost all portions of upper- to mid-septum which could be recorded by cross-sectional echocardiography. The mechanism of the abnormal septal motion in complete left bundle-branch block could be examined by comparing the sequence of activation and contraction of the left ventricle in complete left bundle-branch block with that of normal subjects and that during pacing of the right ventricle. Abnormal septal motion of type A and B was similar to that of complete atrioventricular block during right ventricular pacing. Moreover, experimental study disclosed that ventricular activation begins on the right side of the septum and invades this structure from right to left before activating the free wall of the left ventricle in complete left bundle-branch block (Becker *et al.,* 1958; Sodi-Pallares, 1963; Scott, 1965). It is, therefore, suggested that the abnormal septal motion of types A and B is caused by asynchronous contraction of the left ventricle, with delayed activation of the left side of the septum and of the left ventricular free wall. Patients with the pacing catheter tip in the mid-portion of the right ventricle showed abnormal septal motion of type A, while some patients with right ventricular apical pacing showed abnormal septal motion of type B. These data suggest that a different sequence of ventricular activation and contraction is responsible for the difference between type A and B motion (Gomes *et al.,* 1977; Zoneraich *et al.,* 1977).

However, it is also possible that the septal myocardium is damaged to some degree (though not so extensively as in type C) in type A, in contrast to type B. The fact that about 20 per cent and 33 per cent of patients with type A septal motion had abnormal electrocardiographic and vectorcardiographic findings which were compatible with septal infarction supports this possibility (Table). Further study is needed to solve this problem. Abnormal septal motion of type C is almost the same as that seen in extensive septal infarction. The underlying cardiac abnormalities of patients with type C septal motion were largely myocardial infarction or congestive cardiomyopathy. A high proportion of patients with abnormal septal motion of type C also had abnormal electrocardiographic and vectorcardiographic findings which were compatible with extensive septal infarction with complete left bundle-branch block (Chapman and Pearce, 1957; Scott, 1962; Doucet *et al.,* 1966). Thus patients with complete left bundle-branch block and type C motion may have sufficient septal damage to prevent the early posterior motion seen in type A and B patients. It is possible that some patients with type A septal motion may have septal damage to some degree, as mentioned above. The normal septal motion recorded in 2 patients with complete left bundle-branch block could be the result of a peripheral, rather than a proximal, block of the left bundle-branch.

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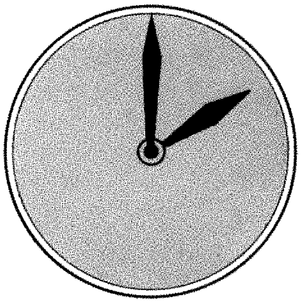

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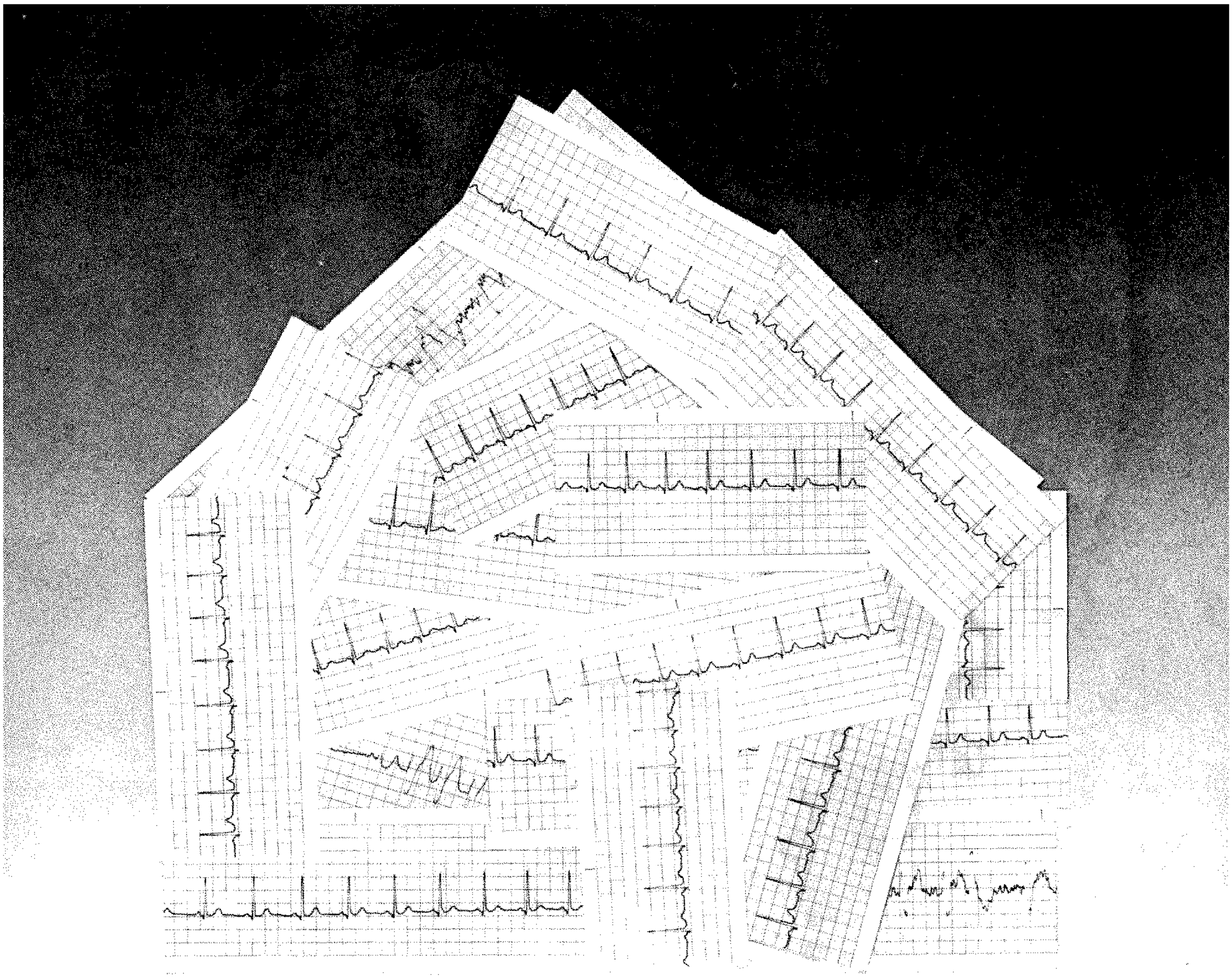

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British Heart Journal, 1979, **42**, 261-265

Diagnosis of left ventricular thrombi by two-dimensional echocardiography[1]

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SUMMARY Sixteen patients had two-dimensional echocardiographic diagnosis of the presence or absence of left ventricular thrombi and anatomical, radiological, or clinical confirmation of the diagnosis. Eleven patients had positive diagnoses, which were confirmed in 10 and possibly incorrect in one. Five other records were reviewed because the patients had undergone aneurysmectomy after two-dimensional echocardiograms: three were true negative and two were false negative studies.

Early experience with M-mode echocardiography suggested that left ventricular thrombi were seldom recognised, though recent reports are more promising (Horgan *et al.*, 1976). There are few series using two-dimensional echocardiography (Ports *et al.*, 1978; DeMaria *et al.*, 1979). In patients with coronary artery disease, the cardiac apex is the site of most left ventricular thrombi (Jordan *et al.*, 1952; Hamby *et al.*, 1974). The recent use of apical and subxiphoid transducer positions for two-dimensional echocardiography has made the apex more accessible for diagnostic assessment. We report our experience in detecting left ventricular thrombi over the past 2½ years, using these techniques.

Subjects and methods

We reviewed the records of all patients who had an initial report written with the diagnostic impression of a 'possible' or 'probable' left ventricular mass suggesting thrombus by two-dimensional echocardiography from June 1976 to December 1978 and who had surgical, angiographic, or clinical confirmation of cardiac thrombi. In addition, records were reviewed to include patients who had undergone two-dimensional echocardiography before resection of left ventricular aneurysms during the last 18 months of the study period.

All patients were examined in the 30° left lateral decubitus position initially, but many were turned into more lateral positions for the apical views. Subxiphoid views were obtained with the patient supine and the knees flexed to attain good relaxation of abdominal muscles. For subxiphoid visualisation, some records were made during sustained or maximal inspiration. A commercially available two-dimensional phased array ultrasonograph (Varian V3000, Palo Alto, CA) was used with a 2·25 MHz fixed focus transducer (Anderson *et al.*, 1977). M-mode recordings were performed using a Smith-Kline Ekoline 20A ultrasonoscope and a 2·25 MHz or 3·50 MHz transducer with 5 cm beam collimation. Initial recordings were made from the left sternal border in long and short axis views as described by Kisslo *et al.* (1976). Apical and subxiphoid views were then performed with particular attention to the left ventricular apex (Chang *et al.*, 1975; Silverman and Schiller, 1978).

We used several criteria for two-dimensional echocardiographic diagnosis of left ventricular thrombi: (1) echocardiographic signs of a mass adjacent to the left ventricular wall, but distinct from the endocardial echo; (2) the texture of the echoes in the mass (frequently) different from the adjacent myocardium; (3) location of the abnormal echo usually near the cardiac apex; (4) asynergic motion of the adjacent ventricular myocardium; (5) imaging of the mass best from the apical or subxiphoid view; (6) occasional mobile projections from the mass into the ventricular lumen (but motion usually synchronous with the adjacent ventricular wall).

The illustrations of two-dimensional echocardio-

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grams in this article are Polaroid pictures of stop-action video tape single frame television images. These images are of significantly lower quality than the display in real time, since only one field of a two field video frame is portrayed. Thus, only one half of the information content on the video tape is displayed by this process, and there is some blurring by the optical system. The motion pattern in real time obviously cannot be appreciated from such pictures.

Results

Eleven patients were identified with a previously made prospective diagnosis of possible or probable left ventricular thrombus. Their clinical characteristics, echocardiographic findings, and method of diagnosis of left ventricular thrombus are listed in the Table. Seven of these patients had confirmation of these findings by surgery or left ventricular angiography. Three further patients had clinical settings suggestive of intracardiac thrombi: one had a stroke, one had multiple systemic emboli, and one had amaurosis fugax. The diagnosis of left ventricular thrombus was unconfirmed in one patient (case 6). He had a negative left ventricular angiogram four months after a positive two-dimensional echocardiogram suggesting left ventricular thrombus. This was regarded as a possible false-positive echocardiographic study.

Table *Clinical, echocardiographic, and diagnostic findings*

Case no.	*Age/ sex*	*Clinical diagnosis*	*Confirmation*	*M-mode*
1	60 F	CAD, S/P MI	Cerebrovascular accident	Possible thrombus (reading influenced by 2D echo findings)
2	41 M	CAD, S/P MI	LV angio +	Negative for thrombus
3	48 M	CAD	LV angio +	Not done
4	70 M	CAD, S/P MI, endocarditis	LV angio +	Negative for thrombus
5	65 M	Aortic stenosis, heart failure	LV angio +, surgery +	Negative for thrombus
6	52 M	Renal failure, CAD	LV angio +	Negative for thrombus
7	66 F	CAD, S/P MI	LV angio +, surgery +	Negative for thrombus
8	45 M	CAD, S/P MI	Amaurosis fugax	Not done
9	56 M	CAD, S/P MI	LV angio +	Negative for thrombus
10	78 M	CAD, S/P MI	Multiple peripheral emboli	Negative for thrombus
11	30 M	CAD, S/P MI	LV angio +	Negative for thrombus

Abbrevations: CAD, coronary artery disease; S/P MI, status post-myocardial infarction; LV, left ventricular.

Examples of two-dimensional echocardiographic images interpreted as showing left ventricular thrombi are shown in Fig. 1–4. The gross specimen of the large apical thrombus imaged in Fig. 4 is

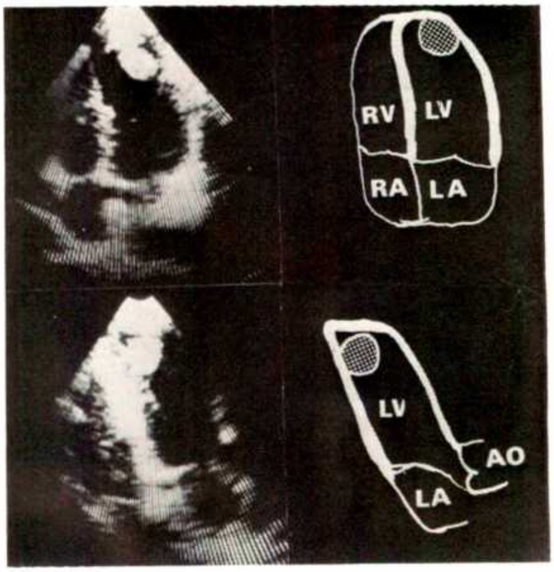

Fig. 1 *Apical four-chamber (above) and apical long axis (below) two-dimensional echocardiographic images (left) from case 3. The stippled circle in the diagrams (right) indicates the abnormal mass of echoes thought to represent a thrombus. AO, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.*

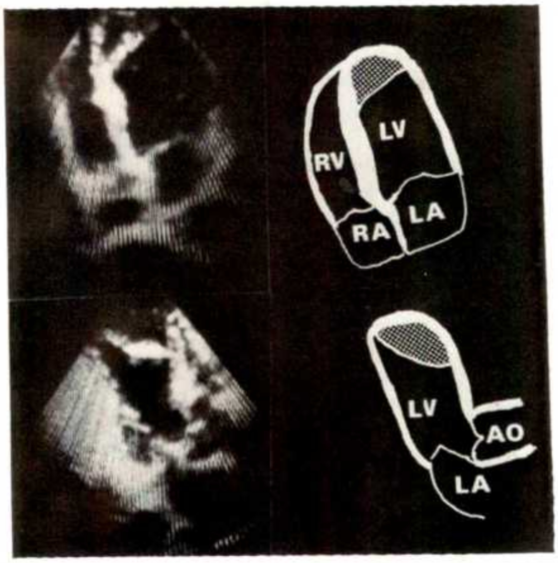

Fig. 2 *Apical four-chamber view (above) and apical long axis view (below) of a left ventricular thrombus (shaded area in diagram at right) in case 4. LV, left ventricle; LA, left atrium; RV, right ventricle, RA, right atrium.*

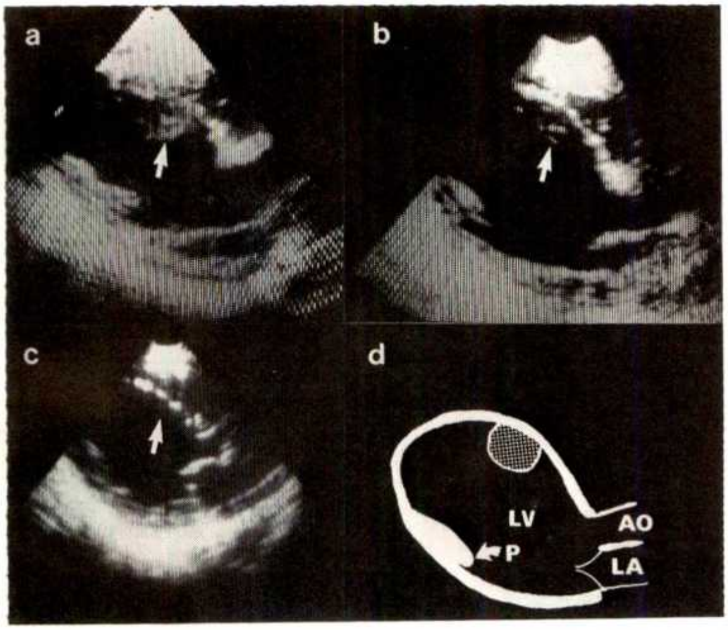

Fig. 3 *Serial long axis views in case 1 showing disappearance of left ventricular thrombus:* (a) *May 1977, showing thrombus (arrow) as shaded in panel d.* (b) *March 1978, with smaller mass of echoes (arrow).* (c) *December 1978, no further abnormal echoes in area of arrow. LV, left ventricle; P, papillary muscle; AO, aorta; LA, left atrium. (Note: Panel c appears different from a and b because of the altered method of video recording of original images.)*

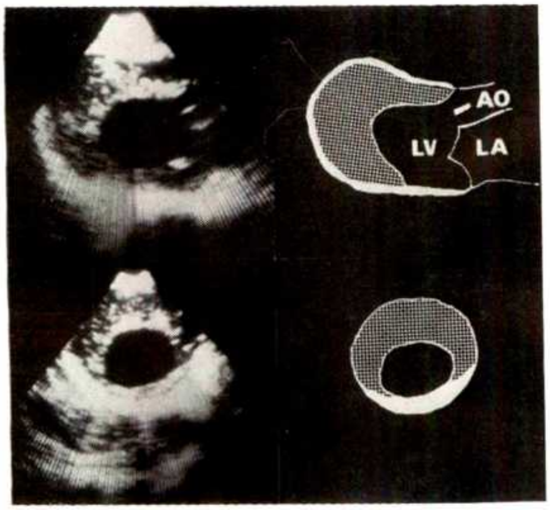

Fig. 4 *Long axis (above) and short axis (below) images of 2D echocardiogram from case 7. Shaded areas in diagrams at right represent thrombus, dense white areas indicate myocardium underlying the thrombus. LV, left ventricle; LA, left atrium; AO, aorta.*

shown in Fig. 5, after successful removal at aneurysmectomy. The specimen is sliced in a plane similar to the ultrasonic plane of imaging. The M-mode echocardiogram in this patient (Fig. 6) did not suggest left ventricular thrombus.

Four patients had serial two-dimensional echocardiograms over a period of several months. In case 1 a mass in an apical aneurysm was unchanged two months after initial study, much smaller at 10 months, and gone at 19 months (Fig. 3). Initial study in case 3 showed two separate apical masses, and over the follow-up period of 10 months the larger one gradually resolved and the smaller remained constant.

Separately, we reviewed records of all patients undergoing left ventricular aneurysmectomy or aneurysm plication during the period from June 1977 to December 1978. Of the 54 patients in this category, six had preoperative two-dimensional echocardiographic studies. One of these had a positive preoperative two-dimensional echocardiogram and is included in the Table (case 7). Three patients had negative two-dimensional echocardiograms confirmed by lack of thrombus at surgery. Two patients had false-negative preoperative two-dimensional echocardiograms. One of these was a 30-year-old man with a traumatic apical aneurysm caused by a knife wound. Apical anatomy was distorted as a result of the initial trauma and two subsequent cardiac operations. On current review of the echocardiogram, echoes possibly representing the apical thrombus were found to be present. Another false-negative study was recorded on a 66-year-old man with an apical aneurysm. Very limited apical and no subxiphoid views were recorded; on review, echoes suggesting apical thrombus were seen in the apical view.

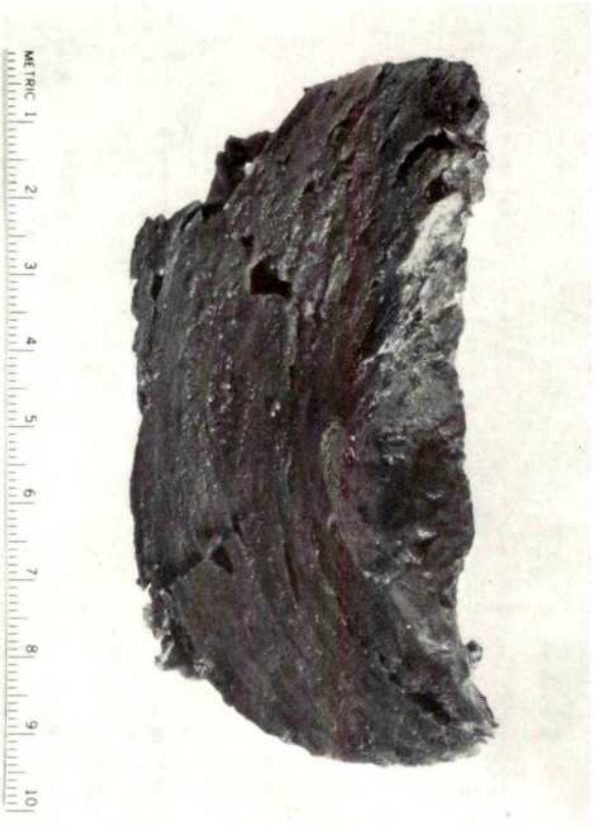

Fig. 5 *Gross specimen of left ventricular thrombus imaged in Fig. 4. Thrombus is sectioned in a plane similar to the upper panel of Fig. 4.*

Discussion

Contrast left ventriculography is the primary tool for diagnosis of mural thrombi but its specificity and sensitivity for this diagnosis are poorly defined in the published reports (Hamby *et al.*, 1974). Thus, it is difficult to assess the accuracy of echocardiographic methods for recognition of mural thrombi unless they are compared with direct pathological examination. In our small series of prospective interpretations two-dimensional echocardiographic findings correctly suggested the diagnosis in 10 of 11

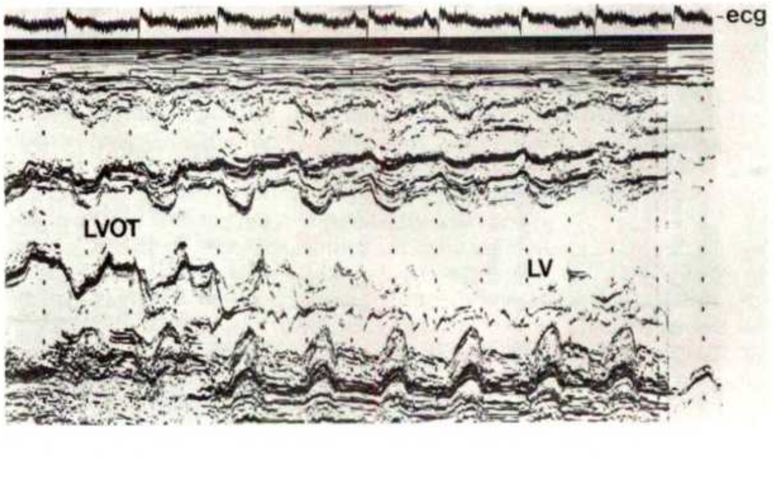

Fig. 6 *M-mode echocardiographic sweep from the left ventricular outflow track (LVOT) to the left ventricular body (LV) in case 7. The large thrombus seen in Fig. 4 and 5 cannot be recognised from this M-mode study.*

positive readings. The usual lack of findings to suggest a mural mass on M-mode records underlines the advantage of the two-dimensional method. We consider the findings in case 6 to have been a possible false-positive since a negative angiogram was found four months after the echocardiogram. Unfortunately, an echocardiogram was not done at the time of the angiogram, and we have assumed the angiogram accurate for this purpose. There was no clinical evidence of embolism between the two studies. A left ventricular thrombus might dissolve during this period. We followed four patients serially (cases 1, 3, 8, 11) for periods from two to 19 months and in two of these cases, with stable masses on the one- and two-month follow-up studies, apparent reduction in size was noted at nine- and 10-month follow-up, respectively; by 19 months the latter patient had no detectable residual mass. This type of information on the natural history of such lesions, available from echocardiography, is desirable for the best management of such patients.

Our experience with false negative and false positive diagnoses of ventricular masses makes us interpret the findings in each new case with considerable conservatism. Several 'artefacts' may simulate the appearance of intracavitary masses. Strong echo reflectors within the image plane may be spuriously displayed within the cavity because of imperfect beam width (Roelandt *et al.*, 1976). Similarly, strong reflectors either in front of, or behind, the primary imaging plane may be spuriously displayed and suggest a mural mass. The transducer related fixed artefact, most prominent in phased array systems, may cause confusion with an apical mass when apical views are used. In addition, dense highly reflective myocardial scar may produce multiple trailing echoes or reverberations that may mimic a mural mass in any one view, but these artefacts have no consistent pattern of location within the heart with various transducer locations. This phenomenon is seen commonly within the aorta and left atrium resulting from reverberations trailing from the strong aortic wall echoes.

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Displacement of pacemaker leads—a 10-year survey

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SUMMARY Displacement of endocardial pacemaker leads from the initial site at the time of implantation is a major cause of unpredictable pacemaker failure. In this survey, we have made a retrospective study of the effectiveness of the attempts made by two manufacturers to design leads to reduce the frequency of this occurrence. The cumulative displacement records of 5 types of leads (Medtronic types 5818, 6904, 6901, and 6950, and Cardiac Pacemakers Inc. type 4210) have been studied, and show that Medtronic 5818 and 6950, and CPI 4210 leads are superior in this respect.

During the past decade the major problem in permanent pacing of the heart has been premature battery exhaustion. Intensive research on suitable long-lived power sources produced the various kinds of lithium cell, which are predicted to lose power gradually in contrast to the often catastrophic failure of the mercury cell. The subsequent increase in the use of these pacemaker generators employing power sources which promise a longer generator lifetime places greater emphasis on the need to implant leads whose design will permit a problem-free lifetime of the same order as that of the generator. The major problems occurring in the use of endocardial pacemaker leads are displacement of the tip of the lead, fracture of a conductor, high threshold, extrusion, and insulation failure.

There will clearly be a broad range of displacements from the extreme case of movement of the tip into the vena cava to the microdisplacement which may well be attributed to 'high threshold'. In this work we consider only those displacements which have been shown either by *x*-ray examination or by a significant change in the direction of the frontal plane vector of the pacemaker stimulus (Green, 1971). The displacement records of 5 types of leads have been analysed retrospectively over a 10-year period to determine whether some types suffer fewer displacements than others.

Material and methods

Details of the construction of each type of lead used are shown in Table 1 (see also Fig. 1). The Medtronic leads 5818 and 6904 are cylindrical between the electrodes, the main difference between the two types being a reduction in the area of the distal electrode of the 6904 to achieve lower pacing thresholds. The Medtronic 6901 and Cardiac Pacemakers Inc. 4210 leads were specifically designed to reduce the incidence of displacements, the flange behind the distal electrode trapping the tip in the trabeculae until endothelial growth secures a stable position. The design of these two leads is similar but the 4210 has triple-wound helical coil conductors to provide fail-safe protection against fracture of one conductor. In a further attempt to achieve stable fixation of the distal electrode, Medtronic introduced the 6950 lead which has 4 flexible silicone rubber tines as an integral part of the body. These tines are designed to be entrapped firmly in the trabeculae.

The usual procedure in Glasgow (Forbes *et al.*, 1968) for placement of the lead tip has remained unchanged during the 10-year period of the survey. The data reported in this survey were extracted from the computer data bank used in Glasgow for storage of information on all pacemaker operations (Green and Reekie, 1975).

Displacements were often detected within 7 days of initial implantation, before the patient was discharged from hospital, when failure of the

Table 1 *Construction of leads analysed in survey*

Model		*Conductor*	*Distal electrode diameter (mm)*	*Area (mm²)*	*Tip*
Medtronic	5818	Single helix	3·2	53	Plain
Medtronic	6904	Single helix	3·2	15	Plain
Medtronic	6901	Single helix	2·2	11	Flange
CPI	4210	Triple helix	2·3	12	Flange
Medtronic	6950	Single helix	2·2	11	Tines

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Table 2 *Analysis of pacemaker lead failures*

Model	*No. used*	*Lead extrusions**	*Failed conductors*	*Failed insulation*	*Increased threshold*	*Clinical complications†*	*Total displacements*	*Displaced within 12 months*	*Total lead failures*
Medtronic 5818	417	19	21	9	18	20	48	30	135
Medtronic 6904	225	4	10	—	16	14	36	31	80
Medtronic 6901	57	2	1	—	4	—	11	11	18
CPI 4210	145	1	—	—	2	2	6	6	11
Medtronic 6950	95	—	—	—	2	—	6	6	7

* Extrusion of lead at or near wound site. † Including infection of generator site and/or extrusion of the generator.

pacemaker to capture the ventricle was shown on the monitor or during routine electrocardiographic recording. Lateral and anteroposterior *x*-ray films were sometimes sufficient to confirm displacement of the tip of the lead, especially if films obtained immediately after implantation were available for comparison. In patients with little pacemaker dependence, even major displacements sometimes remained undetected until, at a pacemaker clinic visit, a change in the direction of the frontal plane vector of the pacemaker stimulus artefact was observed (Green, 1971), indicating a displacement which was subsequently confirmed by *x*-ray examination. However, occasionally small displacements producing loss of capture were not demonstrable on either *x*-ray film or vector evidence, but were confirmed by fluoroscopy when the tip was seen to be mobile within the ventricle.

The records of displacements observed during the use of these leads were analysed using the 'actuarial method' or 'cumulative survival method' introduced to pacemaker analysis by Schaudig *et al.* (1975) and Greatbatch (1975). This method allows the evaluation of the cumulative survival time of the leads without displacement, when the periods of observation differ for each patient. Leads which have been implanted for a certain time without being displaced are included in the survival curve up to that time. In this survey, extending from 1 April 1968 to 31 March 1978, 939 endocardial leads were implanted in 792 patients.

Results

Lead displacement accounted for 42·6 per cent of all lead-related pacemaker failure (Table 2). The risk of displacement is greatest in the period after initial implantation of the lead before the tip is anchored in contact with the endocardium by the growth of fibrous tissue. Displacements within the first 12 months after the initial implant comprised 78·5 per cent of all displacements (Table 2) and this period has been considered in greater detail.

An example of the analyses performed is shown (Table 3) for the Cardiac Pacemakers Inc. (CPI) type 4210 lead after initial implantation. Column A ('incomplete lifetime') shows the number of leads which have not yet reached the end of that 1-month period. Column B ('curtailed lifetime') shows the number of leads ceasing to function for any reason in that 1-month period and includes those displaced leads which were then abandoned rather than re-manipulated; it also includes leads lost to follow-up. Only demonstrable displacements within the

Table 3 *Cumulative stability for CPI 4210 lead after initial implant*

Age (mth)	*(N) Number of leads*	*(A) Incomplete lifetime*	*(B) Curtailed lifetime*	*(D) Number displaced*	*(T) Total (A + B)*	*(X) Number at risk* $\left(N - \frac{T}{2}\right)$	*Fraction displaced* $\left(F = \frac{D}{X}\right)$	*Fraction stable* $(S = 1 - F)$	*Cumulative stability* $\left(CS = 1 - \frac{\Sigma D}{X}\right)$
1	145	5	10	4	15	137·5	0·029	0·971	0·971
2	130	7	3	1	10	125·0	0·008	0·992	0·963
3	120	4	2	—	6	117·0	0	1·000	0·963
4	114	4	1	—	5	111·5	0	1·000	0·963
5	109	8	1	—	9	104·5	0	1·000	0·963
6	100	3	1	—	4	98·0	0	1·000	0·963
7	96	4	3	1	7	92·5	0·011	0·989	0·953
8	89	11	—	—	11	83·5	0	1·000	0·953
9	79	7	—	—	7	74·5	0	1·000	0·953
10	71	12	—	—	12	65·0	0	1·000	0·953
11	59	7	—	—	7	55·5	0	1·000	0·953
12	52	12	—	—	12	46·0	0	1·000	0·953

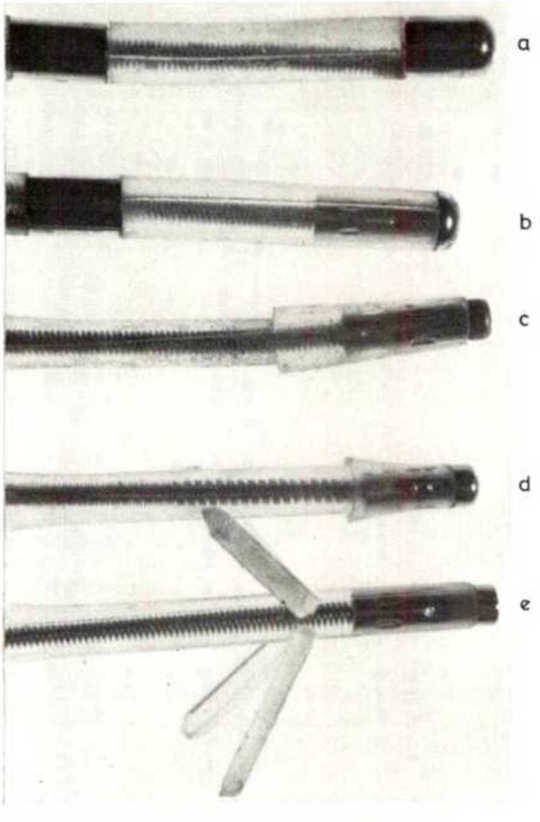

Fig. 1 *Construction of tip of endocardial lead*
(a) *Medtronic 5818,* (b) *Medtronic 6904,* (c) *Medtronic 6901,* (d) *Cardiac Pacemakers Inc. 4210,* (e) *Medtronic 6950.*

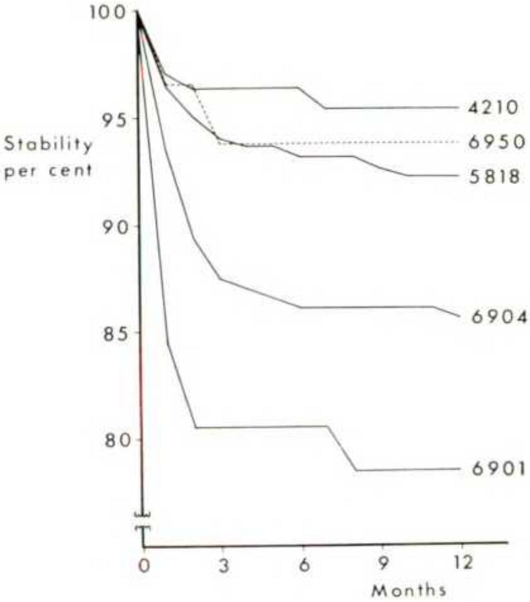

Fig. 2 *Cumulative stability after initial implant.*

right ventricle, into the right atrium, or into the vena cava, have been shown in column D.

The cumulative stability of each type of lead after initial implantation is shown in Fig. 2. For each type there is a relatively high displacement rate in the first 2 months before a more gradual rate of displacement is established over the remainder of the 12 months. The 3 lead types 4210, 6950, and 5818 show a considerably lower displacement rate than the 6904 or 6901 over the first 2 months.

Discussion

The overall rate of demonstrated displacement of endocardial leads in Glasgow is 11·3 per cent which is similar to the average value found from other reports (Table 4). It is essential to have a clear definition of lead displacement since, though many displacements are apparent on the *x*-ray film, a number can be shown only by careful fluoroscopic examination. Minute displacements of the catheter tip are impossible to differentiate from tissue reaction at the tip, since with both an increased stimulation threshold is found at reoperation. Many of the reports summarised in Table 4 fail to specify the criteria used to determine displacement of the lead. The position of the tip of the lead was

Table 4 *Published displacement rates*

Authors	*Number of leads*		*Displacement rate per cent*
Berning and Larsen (1977)	130		20·8
Bette *et al.* (1975)	1085		11·4
Bilitch (1975)	569		18·0
Buffle (1976)	98		15·0
Charles *et al.* (1977)	164		15·9
Edhag (1969)	260		17·3
Grendahl and Sivertssen (1977)	232		11·2
Griesenbeck and Pesendorfer (1975)	323		12·7
Grögler *et al.* (1975)	770		10·1
Haghfelt *et al.* (1974)	176		15·9
Havia *et al.* (1977)	98		11·2
Johansen *et al.* (1977)	159		23·9
Kalmar *et al.* (1975)	672		15·8
Kostiainen (1977)	151		20·5
McGuire *et al.* (1977)	?		11·4
Ohm *et al.* (1977)	213		5·6
Renyi-Vamos *et al.* (1977)	826		17·4
Säuberli *et al.* (1972)	199		17·1
Schaudig *et al.* (1975)	396		18·9
Stertzer *et al.* (1976)	186		3·0
Venere *et al.* (1975)	148		6·3
		Average	14·3
Glasgow	944		11·3

noted by Johansen *et al.* (1977), Kostiainen (1977), and Ohm *et al.* (1977), and Bette *et al.* (1975) and Grendahl and Sivertssen (1977) indicate that displacement was determined by *x*-ray. Only Berning and Larsen (1977) state that they use *x*-ray film and fluoroscopy and would therefore be in a position to identify small displacements not apparent on *x*-ray films alone.

Attempts to design leads which will overcome the problem of displacement appear to have achieved some success. The CPI 4210 lead, introduced in October 1976 and with similar configuration to the Medtronic 6901, has shown a much lower displacement rate, possibly because the triple-wound conductors impart a slightly greater rigidity to the electrode loop in the atrium which helps to maintain contact with the endocardium until fixation occurs. The shorter flange of the CPI 4210 lead will also be trapped within the trabeculae closer to the myocardium. The Medtronic 5818 lead also has a greater rigidity than the Medtronic 6901 and 6904 leads and shows a displacement rate similar to the CPI 4210 and Medtronic 6950 leads. The Medtronic 6950 lead, first used in November 1976, is proving equally successful in preventing lead displacement, especially after fixation by fibrous growth is established, because there is a greater surface area available over which endothelial tissue can grow.

Conclusions

It is increasingly important to make careful measurements at the time of implantation, of stimulation threshold, tissue impedance, and R-wave amplitude as the use of leads of improved design will result in a greater proportion of minute displacements which will be recognised only by the appearance of exit block or by a rapid increase in threshold. Lead displacement has been shown to occur most frequently in the 2-month period immediately after implantation with all 5 types of leads. The new designs of leads are proving effective in reducing the frequency of lead displacement. Follow-up of patients during the weeks after operation is concerned mainly with the possibility of lead failure, but thereafter with the possible occurrence of generator malfunction or clinical complications.

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Assessment of endocardial leads for permanent cardiac pacing

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SUMMARY Catheter tip dislocation is the main complication of permanent pacemaker implantation using the subclavian vein. In this study of 50 patients we compared the incidence of complications using two endocardial electrodes specially designed to prevent tip dislocation. One catheter had a helical endocardial electrode and the other had retractable nylon barbs. The helical electrode was superior in every respect and we recommend its use for pacing through the subclavian vein.

A high incidence of catheter tip displacement has been described using the Devices LC 62 pacing electrode inserted through the subclavian vein (McNeill and Taylor, 1978). This has been ascribed to the obligatory use of narrow-gauge catheters required to negotiate the limited space between clavicle and first rib.

In this study we compare the efficacy of two endocardial electrodes specially designed to minimise the risk of catheter dislocation when the subclavian vein is used for implantation. Catheter tip dislocation is the main complication of pacemaker insertion and in 1976 Sowton reported that it occurred after 10 per cent of implantations in Britain.

Patients and methods

Between March 1978 and January 1979, 50 patients aged between 35 and 90 years (mean 72 years), with symptomatic heart block were given initial pacemaker implants by the subclavian route.

Before implantation the patients were randomly divided into two equally sized groups. One group received 'Vitatron Helifix 23' endocardial pacing catheters (Fig. 1) and the other 'Vitatron MIP 2000' endocardial catheters (Fig. 2a and b).

The procedure has been previously described in detail (McNeill and Taylor, 1978), the catheter being inserted percutaneously under the clavicle using an introducer (Fig. 3). In that description an Argyle Medicut needle was used to gain entry to the subclavian vein. Recently we have found it easier to use the needle accompanying the 'Vygon Desilet-Hoffman FG09 dilator and introducer' set. This introducer is particularly suitable for insertion of the Helifix catheter. The tip of the 'MIP 2000' catheter, however, precludes its use and a special introducer, supplied by the manufacturer, is required.

In all cases the electrode was positioned in the right ventricle at a site where the pacing threshold was under 1 volt. Using the Helifix catheter this often involved waiting a few minutes for the initially high threshold voltage to fall to acceptable limits. Each catheter was attached to a 'Vitalith 6121' pacemaker sited over the right pectoral muscle.

The patients have been followed-up for between 1 and 13 months (mean 7·2 months) after implantation. Both groups of patients were similar in terms of age and duration of heart block and the same physicians implanted an equal porportion of pacemakers within each group.

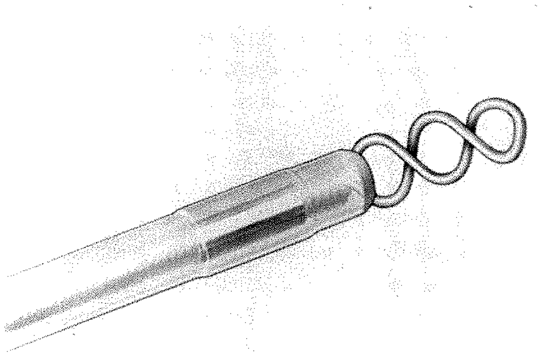

Fig. 1 *Helifix endocardial electrode.*

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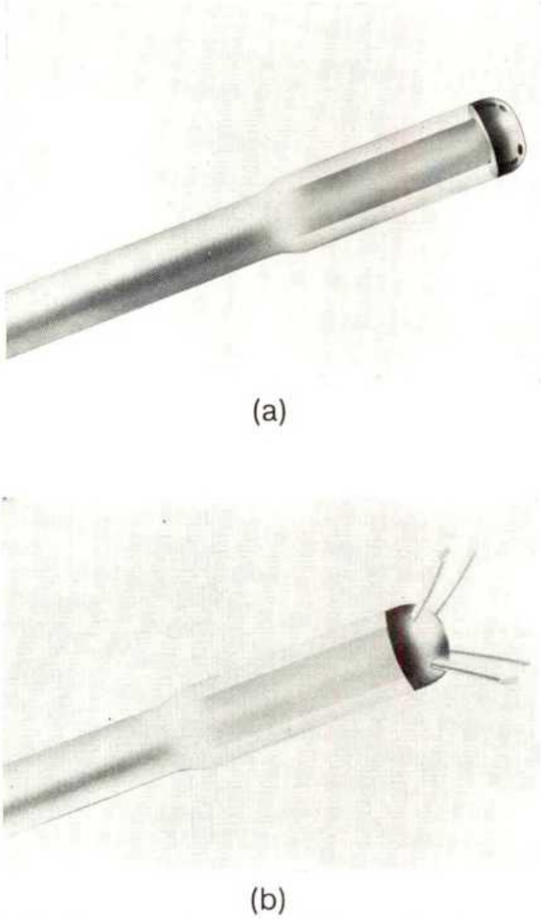

Fig. 2 *MIP 2000 electrode; (a) barbs retracted; (b) barbs projected.*

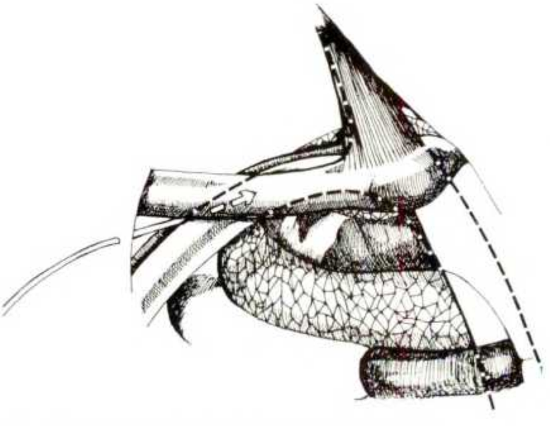

Fig. 3 *Subclavicular subclavian venepuncture.*

Results

The incidence of catheter tip dislocation and pacing failure caused by rising threshold of stimulation are shown in the Table. The Helifix catheter, though occasionally catching the anterior wall of the right atrium, was invariably easier to implant. Insertion of the larger 'MIP 2000' catheter, because of its bulbous electrode tip, frequently led to oozing of blood for a few minutes from the venepuncture site making subsequent catheter manipulation more difficult.

Although 4 patients with 'Helifix' catheters died during the study, death could not be attributed to pacing failure. When necropsies were carried out in 3 of these patients, it was impossible to dislodge the catheter from the right ventricle by traction, the catheters finally breaking just proximal to their distal electrode tips. Unfortunately, when 1 patient in the 'MIP 2000' group died of a myocardial infarction, permission for necropsy was not obtained.

Table *Complications of pacing*

Catheter	*Number of patients*	*Catheter dislocation*	*Rising threshold*
'Helifix'	25	0	0
'MIP 2000'	25	3	4

Discussion

The subclavian vein is a useful portal of entry to the heart for permanent cardiac pacing because it may be used repeatedly and it is constantly sited (Keeri-Szanto, 1956). However, though movement of the arm and neck is not liable to exert traction on a catheter in the subclavian vein, the small space between the clavicle and first rib precludes the use of a very large catheter which would be unlikely to displace from the right ventricle. Though this problem can be overcome by using the supraclavicular approach to the vein this may result in damage to the subclavian artery and phrenic nerve which lie posteriorly to the vein (Epstein *et al.*, 1976).

A possible method of overcoming the problem involves the use of catheters with electrode tips specifically designed to resist displacement after implantation. Endocardial fixation may be by traumatic or non-traumatic means depending on whether or not the endocardium is perforated. The Vitatron Helifix catheter with its helical unipolar electrode achieves non-traumatic fixation by entanglement in the trabeculae carneae. In contrast the MIP 2000 catheter tip traumatically fixes to the endocardial surface by means of projecting nylon barbs deployed by pressure with a guide wire. These are retracted by traction on a nylon wire occupying part of the lumen of the catheter.

Examples of other electrode tip designs range from simple 'shouldering' of the distal end of the catheter gaining a very limited degree of non-traumatic fixation, to more invasive traumatic fixation by means of screw-like helices (Biomedix) or terminal projections (Schaldach, Irnich).

Apart from occasional inadvertent subclavian arterial puncture and two pneumothoraces, none of the various complications associated with subclavian venepuncture has occurred in over 500 subclavicular venepunctures performed in our department. We have found the 'Vitatron Helifix 23' endocardial pacing catheter superior to the 'MIP 2000' pacing catheter in all respects. The Helifix catheter is easily inserted into the subclavian vein and through the tricuspid valve. The helical electrode anchors the catheter firmly in the right ventricle and, in our experience, pacing failure caused by a rising threshold of stimulation has not been a problem.

After implanting pacemakers through the cephalic, axillary, and subclavian veins we have found that implantation by the subclavicular subclavian route using a 'Vitatron Helifix 23' endocardial lead to be the most reliable and easily performed method of permanent cardiac pacing.

We are indebted to Dr Hamish Watson for advice.

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Electrophysiological properties of right heart and atrioventricular conducting system in patients with alcoholic cardiomyopathy

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SUMMARY In 20 men with alcoholic cardiomyopathy, right atrial and right ventricular monophasic action potential, relative repolarisation rate of phase 3, and effective refractory period were studied, as well as atrioventricular conduction properties. The duration of right atrial monophasic action potential and effective refractory period recorded in the middle of the right atrium was shorter in comparison with control patients while the right atrial relative repolarisation rate phase 3 was unchanged. In 5 patients with atrial fibrillation, after conversion to sinus rhythm, great variations were found between right atrial monophasic action potential duration at 90 per cent and 50 per cent repolarisation, atrial effective refractory period, and right atrial relative repolarisation rate of phase 3 recorded in 3 different sites of the right atrium. The right ventricular monophasic action potential duration at 90 per cent repolarisation was longer, while right ventricular monophasic action potential duration at 50 per cent, and right ventricular relative repolarisation rate of phase 3 were shorter in alcoholics compared with the control group. The greatest differences between right ventricular monophasic action potential duration and ventricular effective refractory period obtained in 3 different sites of the right ventricle was observed in alcoholics with frequent ventricular premature beats.

The alcoholic patients showed PR prolongation in 35 per cent of cases and intraventricular conduction defects in 50 per cent of cases. In 11 patients His bundle electrograms and atrial pacing showed latent conduction disturbances proximal and distal to the bundle of His.

Chronic ethanol ingestion has been found to have deleterious effects on cardiac rhythm and conduction, quite apart from leading to nutritional deficiency (Regan, 1971). Though arrhythmias and conduction disturbances are frequently seen in alcoholics (Evans, 1959; Sereny, 1971), to the best of our knowledge there are only limited electrophysiological data in these patients.

The purpose of this paper is to evaluate the electrophysiological properties of the right heart and the atrioventricular conducting system in patients with alcoholic cardiomyopathy. The patients were investigated with the aid of monophasic action potential recordings, atrial and ventricular pacing, and His bundle electrograms.

Subjects and methods

Twenty men aged between 24 and 49 years were studied. All had drunk spirits for more than 10 years and showed criteria for alcoholic cardiomyopathy (Burch and Giles, 1976). The patients had no clinical features of nutritional heart disease, were on an adequate diet, and had no coronary heart diseases or other primary or secondary heart muscle disease. The laboratory data were non-contributory. None of the patients had been taking cardioactive drugs for at least 4 days before the investigation, nor was premedication given. After informed consent, monophasic action potential recordings were obtained with a bipolar suction electrode catheter passed percutaneously to the right chambers of the heart (Gavrilescu *et al.*, 1972; Puech *et al.*, 1974). His bundle electrograms were recorded using a tripolar electrode, introduced via the right femoral vein (Scherlag *et al.*, 1969). A bipolar electrode was introduced via the brachial or femoral vein into the high right atrium. The atrium was paced up to the rate at which type I (Wenckebach) atrioventricular block occurred. Atrial, ventricular, and atrioventricular nodal refractory

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periods were assessed using the extrastimulus method (Wit *et al.*, 1970) with a basic cycle length of 600 ms and the extrastimulus of twice diastolic threshold delivered after every 8th beat. His bundle intervals were measured in sinus rhythm and during atrial pacing. The refractoriness of the right atrium and ventricle was measured during pacing of the heart by the monophasic action potential electrode catheter (Brorson, 1975).

Fifteen subjects aged between 27 and 45 years with non-specific heart or thoracic disorders in whom electrophysiological studies were performed to rule out organic heart disease acted as a control group. The monophasic action potentials were recorded from the mid-right atrium and from the lateral right ventricular wall in all patients. In 3 subgroups of these subjects the monophasic action potentials and investigation of refractoriness were performed from the high, middle, and low right atrium and from the apex, the lateral wall, and the base of the right ventricle:

Group 1 included 5 patients with alcoholic cardiomyopathy who had atrial fibrillation converted to sinus rhythm, and no more than 6 ventricular extrasystoles a minute.

Group 2 consisted of 3 patients with alcoholic cardiomyopathy in stable sinus rhythm with less than 6 ventricular extrasystoles a minute.

Group 3 included 4 of the controls. The monophasic action potentials were analysed according to Brorson (1975) and Cabasson *et al.* (1975). All calculations were performed from 10 complexes and the measurements were expressed as mean values.

Results

In the 20 patients with alcoholic cardiomyopathy, 7 demonstrated ST-T segment changes previously regarded as specific (Evans, 1959), and 4 exhibited non-specific ST-T abnormalities. Significant changes in the electrophysiological properties of the atrioventricular conduction system were found. Arrhythmias and conduction disturbances were common in these patients (Table 1). In 3 patients with chronic atrial fibrillation DC shock was successful, but in 2 cases it was not followed by sinus rhythm. In the case with complete atrioventricular block associated with atrial fibrillation and syncopal attacks, the conduction was interrupted proximal to the bundle of His; 2 patients wth normal PR interval had prolonged His-Purkinje conduction times. In 6 patients the HV prolongation was associated with bundle-branch block or fascicular blocks. During atrial pacing at increasing rates, a first group of 7 patients with prolonged PR interval developed the Wenckebach phenomenon proximal to the bundle of His at relatively slow rates (between 112 and 138 beats a minute), showing altered intra-atrial or atrionodal conduction. During spontaneous sinus rhythm the AH interval was within normal limits in 3 cases in this group. A second group of 6 patients with normal PR interval and normal atrionodal conduction time developed a similar Wenckebach phenomenon at a similar pacing rate (between 129 and 135 beats a minute), suggesting latent conduction disturbances in the atrioventricular nodal area. In a third group of 5 patients with normal PR and AH intervals atrial pacing could be increased above 145 beats a minute. The mean effective refractory period of the atrioventricular node in the first group was 387 ms ±20, in the second group 353 ms ±7, and in the third group 330 ms ±98. These values were significantly prolonged compared with a control group (mean 294 ms ±7).

Table 1 *Arrhythmias and conduction disturbances found in 20 patients with alcoholic cardiomyopathy*

Chronic atrial fibrillation	6	
Paroxysmal atrial fibrillation	2	
Paroxysmal atrial flutter	1	
Ventricular premature beats >6/min	10	
First degree atrioventricular block	7	
Intra-atrial + infra-Hisian		1
Atrionodal		3
Atrionodal + infra-Hisian		1
Infra-Hisian		2
Complete heart block with atrial fibrillation	1	
Left bundle-branch block	5	
Left anterior hemiblock	3	
Left posterior hemiblock	1	
Right bundle-branch block	1	

The following terms were used in order to evaluate the electrophysiological properties of the heart:

(1) The duration of the right atrial and ventricular monophasic action potential complexes measured at 90 per cent and 50 per cent of repolarisation.

(2) The relative repolarisation rate of phase 3 of the right atrial and right ventricular monophasic action potential complexes. This represents the difference in time between 50 per cent and 90 per cent repolarisation (e) expressed as per cent/second using the formula: relative repolarisation rate phase $3 = 40 \times 1000/e$. This index is valuable in assessing phase 3 (Olsson, 1971; Brorson, 1975).

(3) Effective refractory period of the atrium is the longest S_1–S_2 interval at which the premature atrial extrastimulus fails to depolarise the atria.

(4) Effective refractory period of the atrioventricular node is the longest A_1–A_2 interval at which the premature extrastimulus response (A_2) fails to conduct to the His bundle (no H_2).

(5) Effective refractory period of the ventricle is the longest S_1–S_2 interval at which the premature

ventricular extrastimulus fails to depolarise the ventricles.

The schematic illustration of the analyses of a single atrial or ventricular monophasic action potential complex is shown in Fig. 1. Fig. 2 and 3 show examples of the determination of the effective refractory periods in the high, middle, and low right atrium, and in the apex, lateral wall, and base of the right ventricle.

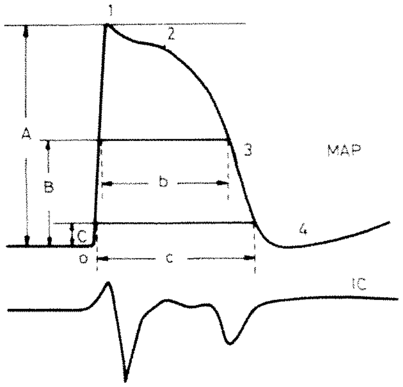

Fig. 1 *Schematic illustration of the analyses of a single monophasic action potential complex (MAP). The amplitude of the MAP was measured and expressed in millivolts* (A). *The duration of the MAP was measured at amplitude of 50 per cent and 90 per cent repolarisation* (B *and* C) *and expressed in milliseconds* (b *and* c); *0, 1, 2, 3, and 4 represents the phases of MAP complex. IC, intracavitary electrogram.*

Comparison of the monophasic action potential complexes recorded from the mid-right atrium between patients with alcoholic cardiomyopathy and the control group showed that the right atrial monophasic action potential duration at 90 per cent and 50 per cent repolarisation and the atrial effective refractory periods were shorter in the patients with cardiomyopathy. No difference was found in the right atrial relative repolarisation rate of phase 3 between these groups (see Table 2). From the right ventricular studies, right ventricular monophasic action potential duration at 50 per cent repolarisation, right ventricular effective refractory period and right ventricular relative repolarisation rate of phase 3 were found to be shorter in the alcoholic cardiomyopathy group. However, right ventricular monophasic action potential duration at 90 per cent repolarisation was longer than in the control group (see Table 2).

Table 3 lists the values of monophasic action potential recordings and effective refractory period determinations obtained from multiple sites from alcoholic patients with atrial and ventricular arrhythmias, as well as from patients with stable sinus rythm and from control subjects. The first group showed the greatest differences in the mean monophasic action potential duration at 90 per cent and 50 per cent repolarisation, right atrial relative repolarisation rate phase 3 per cent/s, and the effective refractory period between the 3 different sites.

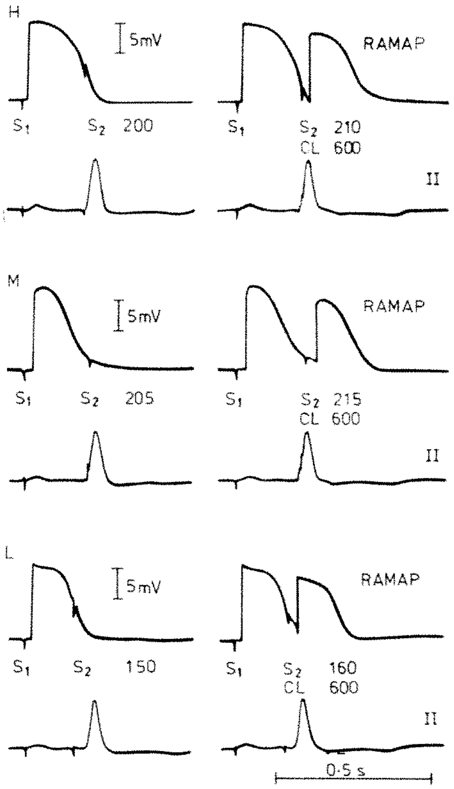

Fig. 2 *Case 15. The right atrial monophasic action potential (RAMAP) obtained in the high (H), middle (M), and low (L) right atrium and the determination of the effective refractory period. S_1, driving stimulus; S_2 testing stimulus; CL, cycle length.*

Discussion

In animals alcohol ingestion produces metabolic disturbances and structural damage as well as depression of myocardial function (Maines and Aldinger, 1967; Opie, 1969; Burch *et al.*, 1971). Alcohol administration in man has been shown to reduce mechanical efficiency of the heart (Mitchell and Cohen, 1970) and to alter the electrocardiogram (Evans, 1959; Gould *et al.*, 1974). Atrial fibrillation,

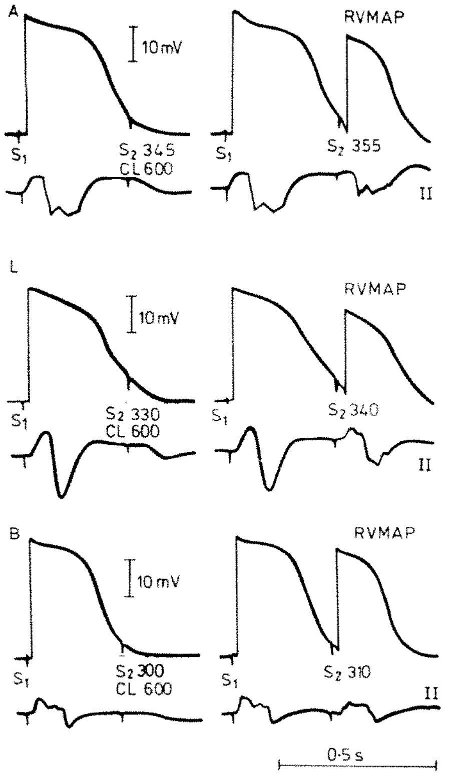

Fig. 3 *Case 5. The right ventricular monophasic action potential (RVMAP) obtained in the apex (A), lateral wall (L), and base (B) of the right ventricle and the determination of the effective refractory period. S_1, driving stimulus; S_2, testing stimulus; CL, cycle length.*

paroxysmal atrial tachycardia, ventricular extrasystoles, sometimes in the presence of increased sinus rate, and atrioventricular or bundle-branch block were frequently observed in alcoholic patients with no clinically detectable myocardial disease as well as in those with manifest cardiomyopathy (Regan, 1971; Burch and Giles, 1975). Dimpled, bifid, peaked, or narrowly inverted T waves were thought to be appropriate electrocardiographic ST-T changes but in some cases non-specific ST-T changes could also be seen (Evans, 1959; Sereny, 1971; Regan, 1971).

Our patients represent a series of men between the third and fifth decades of life, chronically consuming large quantities of alcohol and with clinically detectable heart muscle disease. In 6 patients in the advanced stage of the disease, chronic atrial fibrillation has been observed; 3 patients with early cardiomyopathy had paroxysmal atrial fibrillation or flutter. In case 1 atrial fibrillation was associated with complete atrioventricular block, and pacemaker implantation was necessary to improve his haemodynamic state. Most of the patients with advanced stage of the disease and chronic atrial fibrillation also had ventricular extrasystoles.

Monophasic action potential recordings together with the determination of the effective refractory periods enhanced an understanding of the underlying electrophysiological mechanism in our patients. The right atrial monophasic action potential duration at 90 per cent and 50 per cent repolarisation and atrial effective refractory period recorded in the mid-right atrium were significantly shorter in alcoholics than in the control group, while no differences could be observed for the right atrial relative repolarisation rate of phase 3 per cent/s in these 2 groups. These changes probably suggest the shortening of phase 1 and 2 of the action potential, while phase 3 remains unchanged (Hoffman *et al.*, 1959), and may account for the frequency of the atrial arrhythmias in these patients (Hoffman and Cranefield, 1964; Cranefield *et al.*, 1973). Monophasic action potential duration in man is shortened under the influence of hyperthyroidism, catecholamines, digitalis, and in patients in whom atrial fibrillation tends to recur after successful conversion (Olsson, 1971; Cotoi *et al.*, 1972a, b). Thyrotoxicosis and digitalis effects were not present in our case but excessive sympathetic stimulation and catecholamine release could not be excluded. Though we have not assessed the tendency to relapse of atrial fibrillation in our patients and have no data on right atrial monophasic action potential duration before chronic atrial arrhythmias developed, it is plausible that there is a correlation between arrhythmias and shortening of right atrial monophasic action potential duration.

In the group of patients in whom atrial fibrillation had been converted to sinus rhythm, the results of multiple recordings of right atrial monophasic action potential and multiple determinations of the atrial effective refractory period showed nonuniformity of the refractoriness as compared to the patients without atrial arrhythmias and the controls. In this group we found the greatest differences between the values obtained at the three sites in the right atrium. The right atrial relative repolarisation rate of phase 3 per cent/s recorded in the mid-right atrium was similar in alcoholics and in controls. However, greater differences could be seen between values obtained at the 3 sites of the right atrium in alcoholics with atrial arrhythmias in comparison with the others. The lack of homogeneity in the rate of repolarisation favours the occurrence of arrhythmias, particularly atrial fibrillation and ventricular extrasystoles (Wit *et al.*,

Table 2 *Main clinical and electrophysiological data obtained in 20 patients with alcoholic cardiomyopathy and mean electrophysiological values obtained in 15 control subjects*

Case no.	*Sex*	*Age (y)*	*Cardio-megaly*	*Surface ECG*	*PR interval (ms)*	*His bundle intervals (ms)*			*Paced Wenckebach AV block (rate/min)*
						PA	*AH*	*HV*	
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
1	M	49	+ + +	AF, complete AV block LBBB, PVB	—	—	—	65	—
2	M	45	+ +	AF, LAH, NST, VES	215	20	150	45	118
3	M	42	+ +	AF, RBBB, NST	225	20	155	50	125
4	M	47	+ + +	AF, LBBB, VES	—	—	—	65	—
5	M	40	+ +	AF, LBBB, VES	250	30	150	70	115
6	M	24	+ +	LAH	190	30	110	50	155
7	M	32	+	SST	210	35	115	60	130
8	M	38	+	SST	195	25	125	45	135
9	M	41	+ + +	LBBB, VES	220	20	130	70	138
10	M	35	+	SST, VES	180	30	100	50	145
11	M	28	+ +	LAH, NST,VES	150	40	70	40	160
12	M	39	+ +	SST, VES	240	35	155	50	120
13	M	34	+ +	LPH, PAFl	190	40	90	60	132
14	M	44	+ + +	LBBB, VES	210	60	90	60	112
15	M	31	+ +	AF, NST, VES	190	40	90	60	135
16	M	30	+	PAF, SST	190	30	110	50	132
17	M	33	+	Normal	175	25	105	50	158
18	M	29	+	PAF	190	30	100	60	130
19	M	37	+	SST	185	25	120	40	129
20	M	39	+	SST	170	30	95	45	160
Patients									
Mean		37			199	31	114	54	135
SD		2			7	3	17	3	7
SE		2			6	2	6	2	4
No.		20			18	18	18	20	18
Control									
Mean		37			157	19	113	44	185
SD		2			7	3	17	3	7
SE		1			5	1	16	1	6
No.		15			15	15	15	15	15
Significance 5%		NS			S	S	NS	S	S

+, + +, and + + +, minimal, moderate, and gross; AF, atrial fibrillation; LBBB, left bundle-branch block; LAH, left anterior hemiblock; LPH, extrasystoles; SST, specific ST-T changes; NS, not significant; S, significant. Symbols can be deduced from text.

1974). Possible mechanisms include alterations of cell membrane permeability and stimulation of catecholamine secretion from the adrenal medulla by ethanol (Sereny, 1971).

The right ventricular monophasic action potential duration at 90 per cent repolarisation was longer while the right ventricular monophasic action potential duration at 50 per cent repolarisation, and the ventricular effective refractory period, were shorter in alcoholics than in controls. The right ventricular relative repolarisation rates of phase 3 per cent/s were lower than in controls. Such changes suggest that phase 1 and 2 of the action potential in the right ventricle are shortened while phase 3 is prolonged. The modification in phase 3 of the myocardial action potential could be responsible for the T wave abnormality (Sereny, 1971), but the technique of recording the monophasic action potential does not permit analysis of this phenomenon. The patients with ventricular arrhythmias showed the greatest differences in the right ventricular monophasic action potential duration at 90 per cent and 50 per cent repolarisation and of the ventricular effective refractory period recorded at multiple sites, though such differences were not found for the right ventricular relative repolarisation rate of phase 3 per cent/s. These local differences in conduction properties and refractoriness in right atrium and ventricle fit the experimental data and may be a factor favouring re-entry (Hoffman and Cranefield, 1960). The changes could be explained by non-uniform histopathological damage of the myocardium and are probably non-specific (Burch and Giles, 1976).

Studies in dogs receiving ethanol, without protein or vitamin deficiencies, have shown significant prolongation of the His-Purkinje conduction time compared with that in controls (Ettinger *et al.*, *Paced cycle length (600 ms)*

RAMAP 90% (ms)	*RAMAP 50% (ms)*	*RARRR phase 3 %/s*	*RVMAP 90% (ms)*	*RVMAP 50% (ms)*	*RVRRR phase 3 %/s*	*AERP (ms)*	*AVERP (ms)*	*VERP (ms)*
11	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*
—	—	—	340	255	471	—	—	310
215	105	364	330	240	444	180	360	300
210	100	364	335	240	421	185	390	335
—	—	—	340	260	500	—	—	320
215	110	381	350	250	400	180	410	330
210	105	381	345	265	444	195	335	300
230	120	364	330	260	571	200	390	315
205	110	381	340	250	444	190	365	330
220	120	400	355	220	296	200	415	345
245	125	333	360	270	444	220	350	320
230	130	400	335	275	667	205	315	305
220	115	364	330	240	444	180	385	290
220	140	500	325	235	444	185	350	285
230	110	333	340	245	421	200	365	325
220	115	381	350	260	444	205	350	340
225	125	400	345	265	500	180	345	310
240	130	361	330	275	727	210	330	305
220	135	471	335	285	800	185	350	320
220	120	400	320	265	727	205	360	285
230	130	400	310	245	615	215	320	280
222	119	388	337	255	515	196	360	312
4	5	15	6	6	35	4	8	5
2	2	10	3	4	25	3	7	4
18	18	18	20	20	20	18	18	20
241	135	387	323	270	753	230	295	324
4	5	15	6	6	35	4	8	5
4	5	11	5	5	25	3	4	3
15	15	15	15	15	15	15	15	15
S	S	NS	S	S	S	S	S	S

left posterior hemiblock; NST, non specific ST-T changes; PAF, paroxysmal atrial fibrillation; PAFl, paroxysmal atrial flutter; VES, ventricular

1970). Conduction disturbances are common electrocardiographic findings in about one-third of alcoholics and include varying degrees of atrioventricular block and left or right bundle-branch block (Regan, 1971). In cardiomyopathy the conduction defects are believed to be diffuse and the lesions fibrotic (Stapleton *et al.*, 1970). In a series of 70 patients, 90 per cent of whom had alcoholic cardiomyopathy, Bashour *et al.* (1976) found first degree atrioventricular block in 40 per cent, left bundle-branch block in 6 per cent, left posterior fascicular block in 2 per cent, and 'bifascicular block' in 13 per cent. His bundle electrograms were performed in only a few of these cases. The incidence of the PR prolongation in our patients was 35 per cent, while intraventricular conduction defects were found in 50 per cent. On the surface electrocardiogram 83 per cent of patients with moderate and gross cardiomegaly showed different types of atrioventricular block, while only 25 per cent of patients with minimal cardiomegaly had such conduction disturbances. During electrophysiological studies each alcoholic patient had longer atrioventricular effective refractory periods than the controls, though some patients showed normal atrioventricular nodal conduction times on His bundle electrograms.

Our data show that in alcoholic patients conduction disturbances are frequent and localised at multiple sites in the atrioventricular conduction system. Electrophysiological studies sometimes showed latent conduction disturbances which were not apparent on standard electrocardiographic tracings.

I wish to thank Professor S. Gavrilescu for advice and helpful criticism, and Drs R. Cristodorescu and C. Streian for referring some of their patients.

Table 3 *MAP and ERP durations obtained in 3 sites of right atrium and right ventricle and maximum differences (%) between mean values in same chamber in 8 alcoholic patients and in 4 normal subjects*

Case no.	*Paced cycle length (600 ms)*											
	RAMAP 90% (ms)			*RAMAP 50% (ms)*			*RARRR phase 3%/s*			*AERP (ms)*		
	H	*M*	*L*	*H*	*M*	*L*	*H*	*M*	*L*	*H*	*M*	*L*
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
Group 1 patients												
2	180	215	255	90	105	180	444	364	533	170	180	230
3	180	210	230	85	100	150	471	364	571	165	185	210
5	190	215	240	100	110	165	444	381	533	180	180	235
15	210	220	165	180	115	135	1333	381	1333	200	205	150
18	205	220	250	110	135	175	421	471	533	190	185	230
Mean	193	216	228	113	113	161	623	392	701	181	187	211
MD (%)		15			30			44			14	
Group 2 patients												
6	200	210	235	130	105	125	571	381	364	200	195	215
7	215	230	230	140	120	175	533	364	727	220	200	235
8	210	205	225	140	110	145	571	381	500	215	190	200
Mean	209	215	230	137	112	148	559	375	530	212	195	217
MD (%)		9			25			33			10	
Group 3 controls												
	220	240	250	130	130	155	444	364	421	215	235	240
	240	260	270	125	145	165	348	348	381	230	250	250
	230	245	255	145	135	170	471	364	471	220	235	240
	235	250	250	170	160	150	615	444	400	225	235	240
Mean	231	249	256	142	142	160	383	380	418	222	239	242
MD (%)		10			11			9			8	

H, M, and L are high, middle, and low right atrium; A, L, and B are apex, lateral wall, and base of the right ventricle; MD is maximum differences between values obtained in the 3 sites. The other symbols are similar to Table 2.

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RVMAP 90% (ms)			*RVMAP 50% (ms)*			*RVRRR phase 3 %/s*			*VERP (ms)*		
A	*L*	*B*	*A*	*L*	*B*	*A*	*L*	*B*	*A*	*L*	*B*
14	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*23*	*24*	*25*
350	330	300	250	240	210	400	444	444	320	300	280
360	335	330	270	240	250	444	421	500	350	335	310
365	350	310	255	250	220	364	400	444	345	330	300
355	350	320	250	260	230	381	444	444	350	340	320
330	335	310	260	285	250	444	800	667	315	320	300
352	340	314	357	255	232	407	502	500	336	325	302
	10			10			19			10	
320	345	320	250	265	250	571	444	571	300	300	310
330	330	325	260	260	245	571	571	571	305	315	310
325	340	320	230	250	250	471	444	571	315	330	320
325	338	322	247	258	248	538	487	571	307	315	313
	5			5			15			3	
340	320	330	260	260	240	500	667	444	330	340	315
355	360	350	290	305	280	615	727	571	350	345	340
330	315	325	270	265	260	500	800	615	320	325	210
300	295	300	240	245	250	666	800	800	290	305	300
331	322	326	265	268	257	571	748	608	323	329	316
	3			4			24			4	

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Nomogram to calculate oxygen consumption

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SUMMARY A nomogram has been devised for the rapid derivation of the oxygen consumption from the expired minute volume and the fractional concentrations of expired CO_2 and O_2.

The oxygen consumption is a prerequisite for determining the cardiac output by the Fick method. It is obtained after breathing room air for a known period of time, by measuring the minute volume, and the fractional concentrations of carbon dioxide, and oxygen of the expired air.

As the calculation of the oxygen consumption is a tedious one to perform, a nomogram has been devised to help. The nomogram may also be useful in cross-checking rapidly a large number of calculations.

Theory

Oxygen consumption = volume of inspired − volume of expired oxygen, or

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$$\dot{V}O_2 = \dot{V}_I \times F_{I\,O_2} - \dot{V}_E \times F_{E\,O_2} \ldots\ldots (1)$$

where $\dot{V}O_2$ = oxygen consumption (l/min)
$\dot{V}_I$ = inspired volume of air (l/min)
$F_{I\,O_2}$ = fractional concentration of inspired O_2 = 0·2093
$\dot{V}_E$ = expiratory minute volume of air (l/min) measured at ATPS
$F_{E\,O_2}$ = fractional concentration of expired O_2.

Since, in a steady state the body neither prod nor consumes nitrogen, inspired volume of gen = expired volume of nitrogen, or

$$\dot{V}_I \times F_{I\,N_2} = \dot{V}_E \times F_{E\,N_2} \ldots\ldots\ldots (2)$$

Table *Conversion factors to reduce saturated gas volume at ambient temperature and pressure to STPD*

T°C \ *P mmHg*	*700*	*705*	*710*	*715*	*720*	*725*	*730*	*735*	*740*	*745*	*750*
15	0·857	0·863	0·870	0·876	0·882	0·888	0·895	0·900	0·907	0·913	0·919
16	0·853	0·859	0·866	0·872	0·880	0·884	0·890	0·897	0·903	0·909	0·915
17	0·849	0·855	0·861	0·868	0·874	0·880	0·886	0·892	0·899	0·905	0·911
18	0·845	0·851	0·857	0·863	0·870	0·876	0·882	0·888	0·894	0·900	0·907
19	0·841	0·847	0·853	0·859	0·865	0·872	0·877	0·884	0·890	0·896	0·902
20	0·837	0·843	0·849	0·855	0·861	0·867	0·873	0·880	0·886	0·891	0·900
21	0·832	0·839	0·845	0·851	0·857	0·863	0·869	0·875	0·881	0·887	0·893
22	0·828	0·834	0·840	0·846	0·853	0·859	0·865	0·871	0·877	0·883	0·889
23	0·824	0·830	0·836	0·842	0·848	0·854	0·860	0·866	0·872	0·878	0·885
24	0·819	0·826	0·832	0·838	0·844	0·850	0·856	0·862	0·868	0·874	0·880
25	0·815	0·821	0·827	0·833	0·839	0·845	0·851	0·857	0·863	0·869	0·875
26	0·811	0·817	0·823	0·829	0·835	0·841	0·847	0·853	0·859	0·865	0·871
27	0·806	0·812	0·818	0·824	0·830	0·836	0·842	0·848	0·854	0·860	0·866
28	0·801	0·807	0·813	0·819	0·825	0·831	0·837	0·843	0·849	0·855	0·861

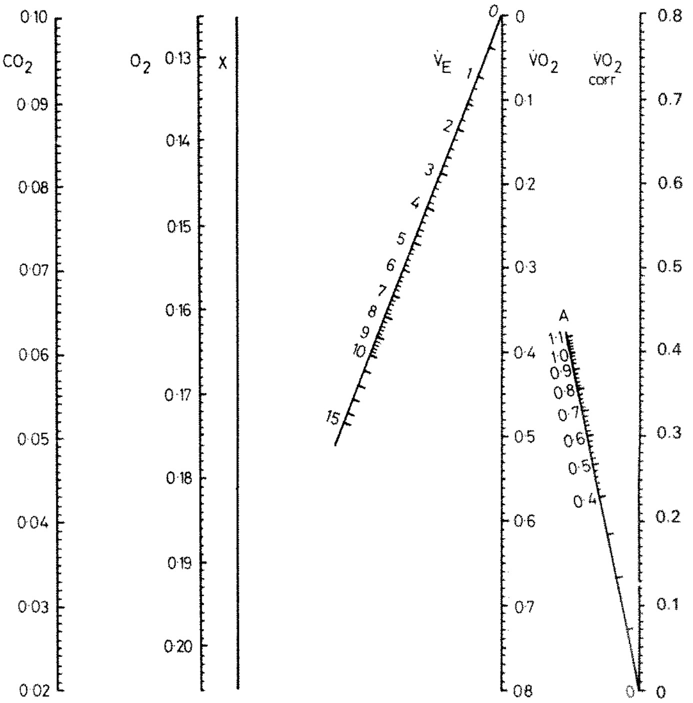

Fig. 1 *Nomogram for estimation of oxygen consumption. CO_2, fractional concentration of expired CO_2; O_2, fractional concentration of expired O_2; V_E, expired minute volume l/min ATPS; V_{O_2}, computed O_2 consumption l/min; V_{O_2} corr, corrected O_2 consumption l/min; A, adjustment factor.*
A straight line joining CO_2 and O_2 intersects the unscaled line x. A second straight line drawn between the point on x and V_E is extended to V_{O_2}. A third straight line is then drawn between the point on V_{O_2} and A to intersect V_{O_2} (corr) to obtain corrected oxygen consumption.

where the fractional concentration of inspired nitrogen ($F_{I\,N_2}$) = 1 − $F_{I\,O_2}$ − $F_{I\,CO_2}$ = 1 − 0·2093 − 0 or 0·7907, as fractional concentration of inspired carbon dioxide ($F_{I\,CO_2}$) is considered to be negligible. $F_{E\,N_2}$ is the fractional concentration of expired nitrogen = 1 − $F_{E\,CO_2}$ − $F_{E\,O_2}$, where $F_{E\,CO_2}$ is the fractional concentration of expired carbon dioxide; or

$$\dot{V}_I = \frac{\dot{V}_E\,(1 - F_{E\,CO_2} - F_{E\,O_2})}{0{\cdot}7907} \quad \ldots.(3)$$

Substituting for $\dot{V}_I$ in equation (1) from equation (3) we get:

$$\dot{V}O_2 = \left[\frac{\dot{V}_E\,(1 - F_{E\,CO_2} - F_{E\,O_2})}{0{\cdot}7907} \times F_{I\,O_2}\right] - \left[\dot{V}_E \times F_{E\,O_2}\right]$$

as $F_{I\,O_2} = 0{\cdot}2093$ we get on simplification:

$$\dot{V}O_2 = (0{\cdot}265 \times \dot{V}_E) - (1{\cdot}265 \times \dot{V}_E \times F_{E\,O_2}) - (0{\cdot}265 \times \dot{V}_E \times F_{E\,CO_2}) \quad \ldots\ldots\ldots\ldots(4)$$

755	*760*	*765*	*770*	*775*	*780*
0·926	0·932	0·938	0·944	0·951	0·957
0·921	0·928	0·934	0·940	0·946	0·952
0·917	0·923	0·930	0·936	0·942	0·948
0·913	0·919	0·925	0·931	0·937	0·944
0·908	0·915	0·921	0·927	0·933	0·939
0·904	0·910	0·916	0·922	0·929	0·935
0·900	0·906	0·912	0·918	0·924	0·930
0·895	0·901	0·907	0·913	0·919	0·926
0·891	0·897	0·903	0·909	0·915	0·921
0·886	0·892	0·898	0·904	0·910	0·916
0·881	0·887	0·893	0·899	0·905	0·911
0·877	0·883	0·889	0·895	0·901	0·907
0·872	0·878	0·884	0·890	0·896	0·902
0·867	0·873	0·879	0·885	0·891	0·897

The expired minute volume ($\dot{V}_E$) is adjusted to standard temperature and atmospheric pressure, i.e. 0°C and 760 mmHg dry (STPD) by the relation.

$$\dot{V}_{STPD} = A \times \dot{V}_E \qquad \ldots.(5)$$

where A is an adjustment factor which can be obtained from the *Documenta Geigy Scientific Tables* (1962), a modification of which is depicted in the Table.

For STPD conditions:

$$A = \frac{273}{273 + T} \times \frac{P - P_{H_2O}}{760} \qquad \ldots.(6)$$

where T = ambient temperature (°C)
P = ambient barometric pressure (mmHg)
P_{H_2O} = water vapour pressure at temperature, T (mmHg).

From (4) and (5) we have corrected $\dot{V}_{O_2}$

$$= A\,[(0{\cdot}265 \times \dot{V}_E) - (1{\cdot}265 \times \dot{V}_E \times F_{E\,O_2}) - (0{\cdot}265 \times \dot{V}_E \times F_{E\,CO_2})] \qquad \ldots.(7)$$

Equation (7) was used to calculate the oxygen consumption depicted in the nomogram in Fig. 1.

Application

With a sharp point of a calliper, mark the fractional concentration of expired CO_2 on the line CO_2 and fractional concentration of expired O_2 on line O_2. Join the two points with a straight line to cross the unscaled line x. By joining the point so obtained on line x and the expired volume ($\dot{V}_E$) on line $\dot{V}_E$ a straight line may be extended to meet line $\dot{V}_{O_2}$ yielding the oxygen consumption (l/min).

The corrected oxygen consumption ($\dot{V}_{O_2}$ corr) may then be obtained by joining the point on line $\dot{V}_{O_2}$ to the adjustment factor A on line A with a straight line and extending it to meet the line $\dot{V}_{O_2}$ corr (example A). If the oxygen consumption is expected to exceed 0·8 l/min, use half the value of $\dot{V}_E$ and double the resultant oxygen consumption (example B). In strenuous exercise it may be necessary to use 1/10th the value of $\dot{V}_E$ and multiply the resultant O_2 consumption by 10.

Examples (Fig. 2)

(A) $F_{E\,CO_2} = 0{\cdot}05$, $F_{E\,O_2} = 0{\cdot}18$, $\dot{V}_E = 5$ l/min, $A = 0{\cdot}9$

Then $\dot{V}_{O_2} = 0{\cdot}120$ l/min, $\dot{V}_{O_2}$ corr $= 0{\cdot}108$ l/min by nomography and calculation.

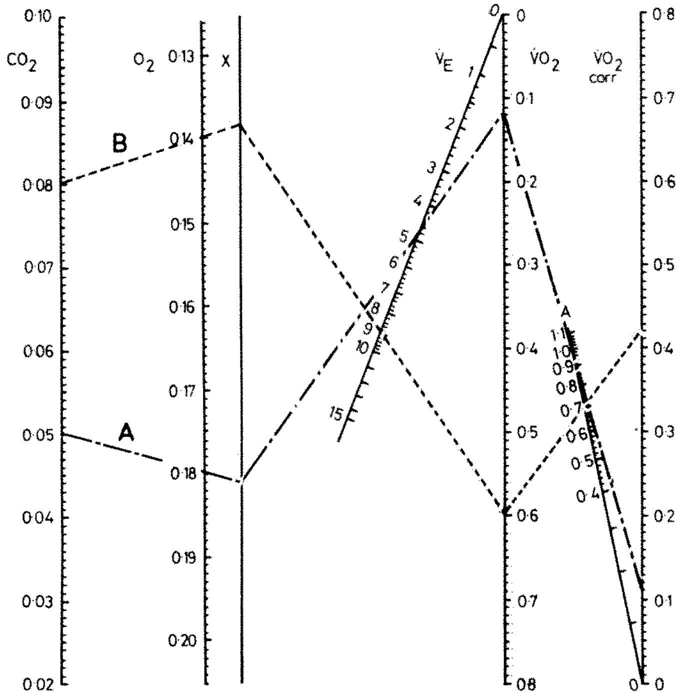

Fig. 2 *Illustrated use of nomogram using two examples as described in the text (A and B).*

(B) $F_{E\,CO_2} = 0{\cdot}08$, $F_{E\,O_2} = 0{\cdot}14$, $\dot{V}_E = 18$ l/min, $A = 0{\cdot}7$

Then $\dot{V}O_2$ corr $= 0{\cdot}420$ l/min from nomogram using $\dot{V}_E = 9$ l/min, $F_{E\,CO_2} = 0{\cdot}08$, $F_{E\,O_2} = 0{\cdot}14$, $A = 0{\cdot}7$.

Hence corrected $\dot{V}O_2 = 2 \times 0{\cdot}420$ or $0{\cdot}840$ l/min when $\dot{V}_E = 18$.

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Value of electrocardiogram in predicting and estimating infarct size in man

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SUMMARY The value of the electrocardiogram in assessing infarct size was studied using serial estimates of the MB isomer of creatine kinase (CK MB) in plasma, serial 35 lead praecordial maps in 28 patients with anterior myocardial infarction, and serial 12 lead electrocardiograms in 17 patients with inferior myocardial infarction. In patients with anterior infarcts, ΣST, ΣR, ΣQ, ΣR/Q+S), and the number of sites with ST elevation more than 2 mm or with QS waves, were obtained from each map. Correlation between both maximum ΣQ and maximum ΣST with cumulative CK MB was highly significant. There was also a significant correlation between ΣR and ΣR/(Q+S) with cumulative CK MB. There was no significant correlation between maximum number of sites with ST elevation or with Q or QS waves and cumulative CK MB. Maximum ΣST and number of sites with ST elevation predicted maximum ΣQ and number of sites with QS or Q waves at a time when infarction was not complete. In patients with inferior infarcts, there was a significant correlation between maximum ΣQ and maxi ΣST in leads II, III, and aVF, and cumulative CK MB.

This study shows that all the waves in the electrocardiogram are useful in assessing infarct The fact that maximum ΣST predicts final ΣQ may be used to assess the efficacy of interventi designed to salvage ischaemic myocardium.

It has been shown that the immediate and long-term prognosis after myocardial infarction is related to the quantity of necrotic myocardium (Sobel *et al.,* 1972; Braunwald, 1976). Experiments in animals now indicate that the size of an infarct may be reduced by appropriate interventions (Maroko and Braunwald, 1973). However, the clinical assessment of interventions designed to protect ischaemic myocardium has posed considerable difficulty. Various techniques (Shell and Sobel, 1976; Bleifeld *et al.,* 1977; Poliner *et al.,* 1977; Muller *et al.,* 1978) have been proposed for measuring and following trends in infarct size in patients.

Electrocardiographic mapping of the infarct from multiple praecordial sites has been proposed for this purpose (Muller *et al.,* 1978). Considerable evidence has accumulated regarding its validity in the experimental situation (Wégria *et al.,* 1949; Kjekshus *et al.,* 1972; Maroko *et al.,* 1972a, b; Hartman *et al.,* 1975; Ross, 1976). However, it has been suggested on the basis of both theoretical evidence (Holland and Brooks, 1975, 1976; Fozzard and Das Gupta, 1976; Holland and Arnsdorf, 1977) and some clinical reports (Norris *et al.,* 1976; Thompson and Katavatis, 1976) that the use of praecordial mapping to measure human infarct has limited value. Most workers have assessed value of individual waves of the electrocardiograp complex (Norris *et al.,* 1976; Selwyn *et al.,* 1977a, b) and there are few data on the QRS complex as a whole and its relation to ST segment changes in the same patient.

The present study was undertaken to investigate further the value of changes in the QRS complex and the ST segment elevation as a guide to infarct size in the coronary care unit. The main aims were to study the relation of the magnitude and extent of Q wave development, R wave loss, and ST segment elevation to each other and to infarct size estimated by calculating the total release of the myocardial isoenzyme of creatine kinase (CK MB) into the plasma.

Patients

Forty-five patients, aged between 46 and 75 years (mean 62·5 years), admitted to the coronary care unit (CCU) of the Radcliffe Infirmary with definite

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evidence of a recent myocardial infarction on a 12 lead electrocardiogram and significant increase in cardiac enzymes, were studied. Patients with intraventricular conduction defects (QRS duration >100 ms) including hemiblocks and second and third degree AV block were excluded. All patients had normal frontal axes (0° to +90°).

Of the 45 patients, 41 gave no history of a previous infarct, and a previous electrocardiogram was available in 14 of these. Twenty-eight patients had anterior infarcts and 17 inferior infarcts; none of the 4 with a history of previous infarction had pathological Q waves on their initial electrocardiogram. Four patients later reinfarcted as shown by new electrocardiographic and enzyme changes. Routine management of the patient was not altered by the study procedure; diuretics and antiarrhythmic drugs were administered as clinically indicated. Lignocaine was given to 8 patients, 11 patients received oral beta-blockers, and disopyramide was used in only 1 patient. No patient had a systolic blood pressure less than 90 mmHg. Three patients required cardioversion for ventricular fibrillation, none of whom showed a further rise in CK MB.

Methods

PRAECORDIAL ELECTROCARDIOGRAPHIC MAPPING

Praecordial electrocardiographic mapping was done in all patients with anterior myocardial infarction. Thirty-five praecordial sites were selected by focusing an ordinary projector beam through a 35 mm slide with 35 holes arranged in 5 horizontal rows and 7 vertical rows. The horizontal rows were designated from top to bottom A to E and the vertical rows from right to left 1 to 7. The distance between the first and second vertical rows was twice the distance between the others to avoid electrode placement on the sternum. With the patient sitting up at 45 degrees, A1 was focused on a point 2·5 cm to the right of the sternal edge in the second intercostal space. E1 was focused 2 cm below the level of the xiphisternum in the same line as A1. The position of the projector was adjusted so that A7 fell on a spot high in the left mid-axillary line in such a way that rows A to E were horizontally placed. All the spots were then marked using indelible ink to allow accurate repositioning of the electrodes each time a recording was obtained.

The electrocardiograms were recorded using a four-channel ink-jet Elema-Schönander Mingograf 34 recorder. Suction cup electrodes with a contact diameter of 15 mm were used. The electrocardiogram was recorded from each praecordial site at 2 different gains simultaneously (1 mV=10 mm and 1 mV=40 mm) so that an accuracy of 0·025 mV could be obtained. Paper speed was 25 mm/s.

Each recording was made during quiet breathing and great care was taken to reposition the patient at the same angle on each occasion. The first recording was obtained at a mean time of 6 hours after the onset of pain (at less than 4 hours in 19 patients, at 4 to 6 hours in 12 patients, at 6 to 12 hours in 10 patients, and at more than 12 hours in 4 patients). Subsequently, recordings were obtained at 8-hour intervals during the first 24 hours, at 12-hour intervals on the second day, and thereafter daily.

Initial studies showed that praecordial electrocardiographic mapping was of limited value in inferior infarction. Therefore, in order to record changes from the inferior surface of the heart, the standard 12 lead electrocardiogram was recorded serially, the V lead positions being marked on the chest wall to obtain reproducible recordings.

ELECTROCARDIOGRAPHIC MEASUREMENTS

Anterior infarct patients

The amplitude of the Q, R, and S waves, and of ST segment elevation (at 60 ms after the J point) was measured in 5 beats from each site, using the TP segment as a baseline. Measurements were made on both the magnified (1mV = 40 mm) and regular recordings (1 mV = 10 mm). These were then summed from 35 leads to obtain ΣR, ΣQ, ΣS, and ΣST. In addition, $\Sigma(Q+S)$ and $\Sigma R/\Sigma(Q+S)$ were calculated for each map.

Inferior infarct patients

In patients with inferior infarction, QII+III+aVF and ST segment elevations in II+III+aVF were calculated.

SERIAL CK AND CK MB ANALYSES

Blood samples were obtained from a peripheral vein through an indwelling cannula at 4-hourly intervals for 72 hours after the onset of pain. Samples were immediately centrifuged for 15 minutes. Plasma was pipetted into plain sterile glass tubes and stored at −20°C. CK was estimated using the method of Oliver (1955) with dithiothreital as activator as utilised by the Searle CPK-UV_{II} kit. The method described by Mercer and Varat (1975) was used to separate the CK isoenzymes.

CK MB and mathematical calculations

The appearance function of CK MB released from the infarcted myocardium was calculated (cumulative CK MB) by the method described by Sobel *et al.* (1972) and modified by Norris *et al.* (1975).

REPRODUCIBILITY STUDIES IN CONTROL SUBJECTS

Twenty normal subjects between the ages of 30 and 70 years, and 5 patients 2 to 4 weeks after infarction, likely to have a stable electrocardiographic pattern, were studied to confirm the reproducibility of praecordial mapping and the standard 12 lead electrocardiogram. Recordings were examined for beat-to-beat variations during sinus rhythm and atrial fibrillation, variations during quiet and deep breathing, variations caused by electrode repositioning, and those resulting from changes in patient position.

The beat-to-beat variation of measurements of the QRS complex and of ST segment elevation in the same recording during sinus rhythm was small (mean 2·2%), compared with a mean of 15 per cent and 20 per cent in 2 patients who were in atrial fibrillation. The variations resulting from changes in posture and during deep breathing were considerable (mean 12·12% and 18·5%, respectively). In contrast, the variation caused by electrode repositioning, day-to-day variation, and variation during quiet breathing with the patient at 45 degrees and in sinus rhythm was less than 5·3 per cent. All patients were in sinus rhythm except 2 who were in atrial fibrillation in whom 10 consecutive beats were averaged.

Results

RELATION BETWEEN CUMULATIVE CK MB AND PRAECORDIAL MAP IN PATIENTS WITH ANTERIOR INFARCTION

ST segment elevation (Fig. 1)

The maximum ΣST observed during the first 3 days was found to correlate significantly with cumulative CK MB ($r=0{\cdot}733$; $P<0{\cdot}001$). There was no significant correlation between ΣST at any other time and cumulative CK MB. The maximum number of recording sites with ST segment elevation more than 1 mm or more than 2 mm also did not correlate with cumulative CK MB.

Q waves

Correlation between the maximum ΣQ and cumulative CK MB was highly significant ($r=0{\cdot}827$; $P<0{\cdot}001$; Fig. 2). No correlation was observed between the number of recording sites showing pathological Q waves ($r=0{\cdot}265$; $P>0{\cdot}1$), or QS waves ($r=0{\cdot}363$; $P>0{\cdot}1$) and cumulative CK MB.

R wave and $R/(Q+S)$ ratio

The inverse relations between minimal ΣR (Fig. 3) and minimal $\Sigma R/(Q+S)$, and cumulative CK MB were less significant ($r=-0{\cdot}623$; $P<0{\cdot}01$ and $r=-0{\cdot}624$; $P<0{\cdot}01$, respectively) than the relation between maximum ΣQ and cumulative CK MB.

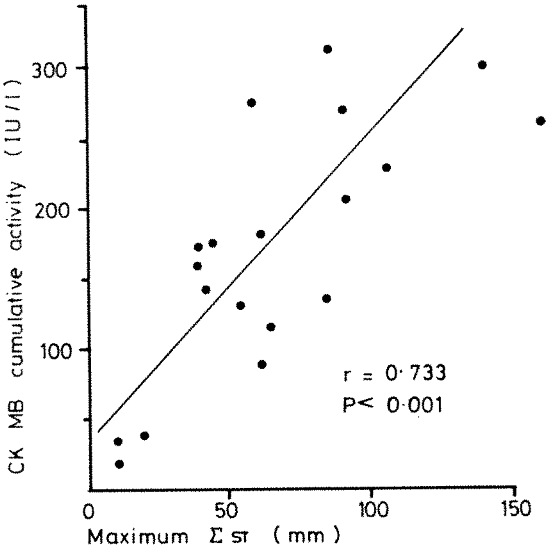

Fig. 1 *Maximum ΣST from the praecordial map is plotted against cumulative release of CK MB in patients with anterior infarction. A good correlation is seen.*

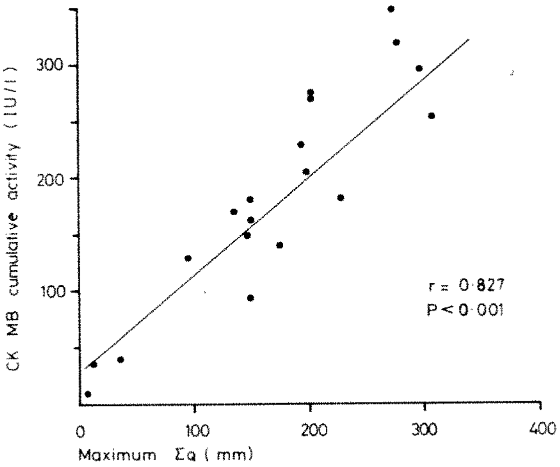

Fig. 2 *Maximum ΣQ is plotted against cumulative release of CK MB in patients with anterior infarction. A highly significant correlation is seen.*

INFERIOR INFARCTION

Preliminary studies not surprisingly failed to show any significant relation between infarct size estimated from CK MB and the praecordial electro-

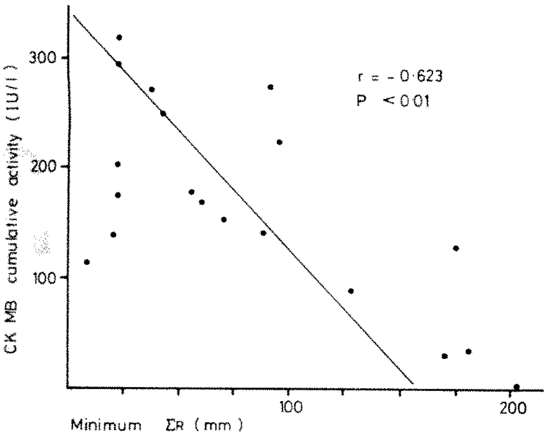

Fig. 3 *Minimum ΣR is plotted against cumulative release of CK MB in patients with anterior infarction. A fair correlation is seen.*

cardiogram in patients with inferior myocardial infarction. However, the sum of the ST segment elevations and of Q wave amplitudes in leads II+III+aVF correlated with cumulative CK MB (r = 0·505; P < 0·05 and r = 0·745; P < 0·01, respectively; Fig. 4). There was no significant relation between the sum of R wave amplitudes in leads II+III+aVF and cumulative CK MB.

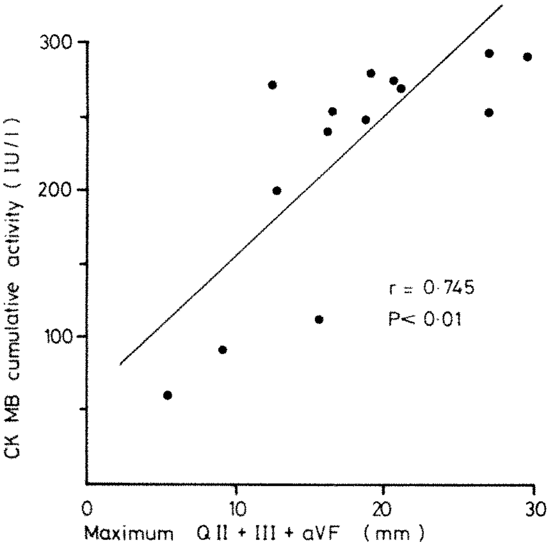

Fig. 4 *Maximum QII+III+aVF is plotted against cumulative release of CK MB in patients with inferior infarction. A fair correlation is seen.*

INTERRELATION OF WAVES IN ELECTROCARDIOGRAM

In patients with anterior infarcts, the maximum ΣST was found to predict maximum ΣQ at a time when electrocardiographic evolution of infarction was not complete (r = 0·820; P < 0·001; Fig. 5). The number of sites with ST segment elevation more than 1 mm and sites with ST segment elevation more than 2 mm predicted the number of sites developing QS waves (r = 0·602; P < 0·01, and r = 0·635; P < 0·01, respectively; Fig. 6). In addition, in individual patients the maximum ST segment elevation recorded at each of the 35 sites correlated well with final Q wave and final R wave amplitude at the same

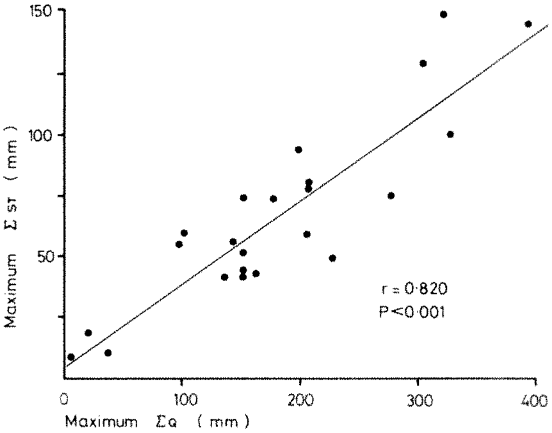

Fig. 5 *Maximum ΣST is plotted against maximum ΣQ in patients with anterior infarction. A good correlation is seen.*

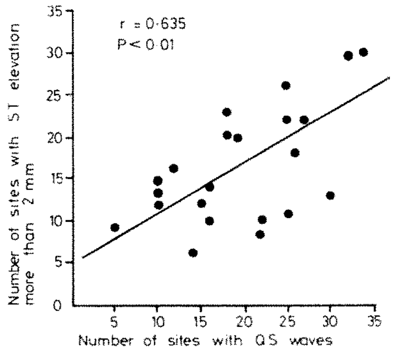

Fig. 6 *The number of sites with ST segment elevation more than 2 mm is plotted against the number of sites with QS waves in patients with anterior infarction. A fair correlation is seen.*

site ($r = 0{\cdot}764$; $P < 0{\cdot}001$, and $r = -0{\cdot}746$; $P < 0{\cdot}001$, respectively). Maximum ΣQ, not unexpectedly, correlated inversely with minimum ΣR in patients with anterior infarcts ($r = -0{\cdot}824$; $P < 0{\cdot}001$).

There was no relation between maximum ST segment elevation and maximum Q II+III+aVF in patients with inferior infarcts.

Discussion

Since Maroko and Braunwald (1973) first described ST segment mapping, considerable interest has been focused on the electrocardiographic method for estimating infarct size. Experimental work in dogs with coronary artery occlusion (Maroko *et al.*, 1972a, b) established the validity of the method. In their animal experiments, the site and, to a certain extent, the size of the infarction was determined by the site of occlusion of a particular coronary artery. However, in the clinical situation, varying sizes of infarct are encountered, more than one wall of the heart may be involved, and evolution of the infarct may be more variable in time (Yusuf *et al.*, 1978).

The development of the enzyme method of estimation of infarct size has provided the clinician with another index of the extent of infarction. Electrocardiographic assessment may be influenced by factors other than infarct size, such as site of infarct, presence of arrhythmias or conduction defects, or changes in local ion concentration; the enzyme method does not have these drawbacks. The amount of CK released has been shown to bear a close relation to total CK depletion in rabbits (Kjekshus and Sobel, 1970), and to infarct size measured morphologically at necropsy in patients who died of acute myocardial infarction (Bleifeld *et al.*, 1977). Though the model for the basis for calculation of infarct size from enzymes has been criticised (Roe *et al.*, 1977), the enzyme method nevertheless provides an empirical estimate of infarct size by a totally independent method, with which electrocardiographic assessment of infarct size can be usefully compared.

ST SEGMENT ELEVATION

The relation of praecordial ST segment elevation to histological and biochemical estimates of the extent of myocardial necrosis is well documented in experimental investigations on animals (Kjekshus *et al.*, 1972; Maroko *et al.*, 1972a, b). However, the relation of ST segment elevation to other estimates of infarct size in man is controversial. Morris *et al.* (1974) showed that ST segment elevation 48 hours after the onset of pain correlated with maximal AST (SGOT) in patients with anterior or inferior infarcts. Blomqvist *et al.* (1975) showed that there was a significant correlation between ΣST and the area of an infarct as determined by pyrophosphate scan. By contrast, Norris *et al.* (1976), Thompson and Katavatis (1976), and Selwyn *et al.* (1977a) showed no correlation or at best weak correlation between ST segment elevation and peak or total plasma enzyme.

In our study we have observed a strong positive correlation between maximum ΣST and cumulative CK MB ($r = 0{\cdot}733$; $P < 0{\cdot}001$) in patients with anterior infarcts, and a weaker but significant correlation in inferior infarcts using the sum of ST segment elevation in leads II, III, and aVF ($r = 0{\cdot}505$; $P < 0{\cdot}05$). Several factors may be responsible for the different results obtained by different workers. Firstly, praecordial mapping reflects only changes affecting the anterior and anterolateral wall of the left ventricle and it is possible that in some studies the patients may have had involvement of other walls of the heart. In our study, none of the patients with anterior infarction had any fresh electrocardiographic changes in the inferior leads, though a small true posterior infarct may have been undetected. Secondly, variations in chest shape and size and localisation of infarction may lead to differences between patients. This ST segment elevation is known to increase or decrease rapidly in some patients (Selwyn *et al.*, 1977a) and variable intervals between onset of pain and time of electrocardiographic recording will introduce further error. To minimise this source of error we have taken recordings at regular intervals in all our patients.

R WAVE

A decrease in the amplitude of R waves during experimental myocardial infarction was reported by Wilson *et al.* (1935). Muller *et al.* (1978) showed a good correlation between loss of R wave amplitude and infarct size in experimental infarction. Recently, Selwyn *et al.* (1977b) have demonstrated a good correlation with estimates of infarct size from CK release.

In our study, we have observed only a fair inverse correlation between minimal ΣR and cumulative CK MB release ($r = -0{\cdot}623$; $P < 0{\cdot}01$). This may be partly the result of the large variation in ΣR observed in our control group of normals (ΣR varies from 150 to 300 mm). Though this may limit the value of ΣR in comparing infarct size in different patients, it is still useful in following the course of infarction in an individual patient (Yusuf *et al.*, 1978), and in comparing infarct size in 2 large groups.

Q WAVE

Myers *et al.* (1948a, b; 1949) described an excellent correlation between the development of Q waves in specific praecordial leads and pathological evidence of infarction in the corresponding areas of the heart. Similarly, in patients undergoing cardiac surgery, as been shown that praecordial Q waves generally verlie epicardial Q waves and that these indicate presence of myocardial fibrosis (Bodenheimer *t al.*, 1976). In addition, a close correlation between praecordial Q waves and ventricular performance in patients with coronary artery disease has been reported (Miller *et al.*, 1972; Williams *et al.*, 1973; Miller *et al.*, 1974; Awan *et al.*, 1977).

These observations are consistent with our finding that ΣQ from praecordial maps correlates well with cumulative CK MB in patients with anterior infarcts ($r = 0{\cdot}827$; $P < 0{\cdot}001$). The range of variation of ΣQ in our control group was between and 12 mm in the 35 lead map. In contrast, ΣQ in most patients with anterior infarcts was several times greater. Though the correlation between QII+III+aVF and cumulative CK MB in patients with inferior infarcts is less impressive ($r = 0{\cdot}745$; $P < 0{\cdot}01$), this is hardly surprising as these data wer obtained from 3 electrocardiographic leads This may detract from its value in comparing t size in different patients but QII+III+aVF useful in comparing groups of patients and in studying the evolution of an infarct (unpublished data).

RELATION OF NUMBER OF SITES WITH E TROCARDIOGRAPHIC ABNORMALITIES TO LATIVE CK MB

gh several workers have used the number of sites (or area) with ST segment elevation or pathological Q wave development as an index of the extent of ischaemia or necrosis and to evaluate the efficacy of interventions (Maroko *et al.*, 1972a, b; Muller *et al.*, 1975; Selwyn *et al.*, 1977a, b; 1978), e found no relation between the number of sites with ST segment elevation greater than 2 mm, ST segment elevation of any degree, or pathological Q or QS waves, and enzyme estimates of infarct size. A similar experience was reported by Nielsen (1973), who observed that the sum of ST segment elevations from an ordinary 12 lead electrocardiogram was a good prognostic indicator, whereas the number of leads with ST segment elevation was t related to prognosis. This is not surprising as number of sites showing abnormalities does not provide information about the magnitude of change at a particular praecordial site. We believe, therefore, that ΣST or ΣQ are better indices of infarct size than the number of sites with abnormalities.

PREDICTION OF INFARCT SIZE

In patients with anterior infarcts, maximum ΣST has been shown to be related to final ΣQ and ΣR, and one could therefore use this measurement to predict infarct size. This relation could also be exploited in assessing interventions aimed at decreasing infarct size, as the slope of the line relating ΣST and ΣQ would be difficult in control subjects and in subjects on beneficial treatment. Henning *et al.* (1978) have used a formula based on ΣST obtained from the first map and the rate of loss of R wave amplitude to predict cumulative CK MB. However, these authors stress that this observation was made in a highly selected group of patients. We have also shown a relation between number of sites with ST segment elevation and those with QS waves. This confirms the work of Askenazi *et al.* (1977) and supports the view that the number of sites with ST segment elevation can be used to predict Q wave extent.

We observed no significant relation between the sum of ST segment elevations in II, III, and aVF, and QII+III+aVF in patients with inferior infarcts.

In conclusion, measurements of ST segment elevation, Q wave development, and R wave loss from praecordial maps, can all be used to assess infarct size in patients with anterior infarcts. Measurements of Q waves and ST segment elevation in leads II, III, and aVF also provide useful but less accurate information about infarct size in patients with inferior infarcts.

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Familial aggregation of coronary heart disease in a high incidence area (North Karelia, Finland)

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SUMMARY Occurrence of coronary heart disease was assessed in families of 211 men under the age of 56 from East Finland. Fifty men were survivors of recent myocardial infarctions, 55 had died of myocardial infarction, 53 suffered from uncomplicated angina pectoris, and 53 were healthy reference men. Overall prevalence of coronary heart disease was similar in families of all case probands. By age 70, case fathers had a 6 times greater cumulative risk (a 36% chance) of dying from coronary heart disease than reference fathers, whereas there was only a small difference between case and reference mothers. Cumulative risk of developing fatal or non-fatal coronary heart disease by age 65 was 4·5-fold for case brothers (70%) and 2·6-fold for case sisters (40%), when compared with reference sibs. The risk was greatest for case sibs with a parental, especially a maternal, history of premature coronary heart disease. Clinical manifestations of coronary heart disease showed similarities within sibships. Cardiac deaths were commonest in sibs of the fatal myocardial infarction probands, whereas angina was commonest in sibs of the angina pectoris probands.

With the precipitous rise in the frequency of coronary heart disease, study of its aetiology has focused on the role of environment; less information has accumulated about genetic factors. The existence of some hereditary basis for coronary heart disease has been recognised, however, in early clinical impressions (White, 1960). Aside from some twin (Cederlöf *et al.*, 1967; Harvald and Hauge, 1970; Liljefors, 1970; De Faire *et al.*, 1975) and population studies (Epstein and Kjelsberg, 1965; Hammond *et al.*, 1971; Sholtz *et al.*, 1975), most of the evidence of a genetic component in coronary heart disease has been derived from case-control studies of families (Gertler and White, 1954; Thomas and Cohen, 1955; Russek and Zohman, 1958; Shanoff *et al.*, 1961; Rose, 1964; Slack and Evans, 1966; Phillips *et al.*, 1974). Though beset with many methodological problems (Haenszel, 1950; Epstein, 1964; Murphy, 1967; Napier *et al.*, 1972), these have uniformly shown a higher frequency of the disease in the families of coronary heart disease cases than in the families of controls.

From what is known it appears that coronary heart disease shows a modest, generally two- to threefold increase in frequency in families of coronary patients. Similar familial concentrations have been found also for most other chronic diseases for which they have been sought (Edwards, 1963). The degree of aggregation of coronary heart disease appears to be greater, however, in families of young patients with coronary heart disease (Shanoff *et al.*, 1961; Slack and Evans, 1966), in particular in fatal forms of the disease (Deutscher *et al.*, 1970). Consequently, in populations known to have a high incidence of fatal coronary heart disease in the young, familial aggregation of coronary heart disease may be more distinct than elsewhere.

Finland is a country with the world's highest morbidity and mortality from coronary heart disease in young and middle-aged men (Epstein and Krueger, 1969). Within the country, pronounced geographical differences exist in the rate of coronary heart disease; the incidence and mortality are highest in the east (particularly in the province of North Karelia).

The objectives of this study were firstly to establish whether, and to what extent, coronary heart disease aggregates within families of relatively young men with coronary heart disease in this area where the incidence of the disease is exceedingly high, and, secondly, to establish whether there are any differences in the degree of aggregation in families of men who develop either non-fatal or fatal myocardial infarction, or angina pectoris.

In subsequent reports, data on the risk factor levels in these families as well as comparison of the

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present findings with those in a region of Finland with a lower incidence of coronary heart disease will be given.

Subjects and methods

PROBANDS

Non-fatal myocardial infarction

The probands were 50 consecutive survivors of myocardial infarction among men under the age of 56 admitted to hospitals during a 2½-year period in 1972 to 1974 in 2 neighbouring communities in North Karelia. The list of myocardial infarction cases was based on hospital records only, but it proved to be identical with the list collected from all available sources by the WHO's myocardial infarction register operating in the same communities (Puska and Mustaniemi, 1975).

The non-fatal myocardial infarction probands had to meet the following criteria: (1) definite myocardial infarction (World Health Organization, 1971), that is either unequivocal electrocardiographic evidence of a recent myocardial infarction, or diagnostic changes in serum enzyme pattern together with either suggestive electrocardiographic changes or a typical history of chest pain; and (2) survival for more than 28 days after the attack, with no fatal recurrence by the end of 1974. Of the 50 eligible men, 16 had had at least 1 clinical myocardial infarction before the present attack. The age of the non-fatal myocardial infarction probands ranged from 33 to 55 years (mean 48·8 years).

Fatal myocardial infarction

The probands were consecutive fatal cases of verified coronary heart disease that occurred among men under age 56 during a 2½-year period in 1972 to 1974 in the same communities as above and in the immediate surrounding area. The death certificates with Code Nos. 410–414 (International Classification of Diseases, Injuries and Causes of Death (ICD), 8th revision) from the study communities were obtained from the Central Statistical Office in Finland. The hospital records, necropsy findings, information from local physicians, and other pertinent data were collected for each case. The cause of death was determined after a review of these documents. The criteria for accepting coronary heart disease deaths were the following: either (1) definite myocardial infarction (World Health Organization, 1971), with survival less than 28 days, or positive postmortem evidence of recent myocardial infarction; or (2) possible myocardial infarction (World Health Organization, 1971), that is cases in which the fatal event was preceded by a history of chest pain as well as either previous symptoms of coronary heart disease or suggestive necropsy findings such as old myocardial infarct scars or severely affected coronary arteries. These criteria were met by 60 men.

The closest relatives of the fatal myocardial infarct probands were sought with the aid of local church, postal, and police personnel, and the search was unsuccessful for only 5 probands.

The age of the 55 fatal myocardial infarct probands included in the study ranged from 22 to 55 years (mean 46·3 years). Before the fatal attack, coronary heart disease had been diagnosed in 38 men, 21 of whom had suffered clinical myocardial infarction. Death was sudden (within 1 hour from the onset of the symptoms) in one-half of the cases. One-quarter of the cases came to necropsy.

Angina pectoris

The probands were screened from the records of occupational health examinations performed between 1970 and 1974 on about 3000 men employed by large wood and paper companies in the same communities from which the other probands were selected. Employees with resting electrocardiographic abnormalities (Minnesota Code Nos. 1.2–3, 4.1–3, 5.1–3, 6.1–2, 7.1–2 or 8.3) (450 men) were examined by the author. Fifty-three men were judged to have clinical angina pectoris without evidence of past myocardial infarction or a secondary cause for angina. These men constitute the angina pectoris probands of this study. ST changes were seen in the resting electrocardiograms of one-half of the selected men, in one-third there were T changes only. Definite coronary heart disease had been diagnosed earlier in 38 men, and 15 of them had retired because of the disease. The duration of angina pectoris symptoms varied from 3 to 99 months. The age of the probands ranged from 27 to 55 years (mean 49·5 years).

Reference men

The reference probands were selected from the same employee rosters as the angina pectoris probands. For each angina pectoris proband, 2 prospective reference men matched for age and marital status were selected from the same occupational speciality. The one of the two whose date of birth was closest to that of the respective angina pectoris proband was finally selected unless he had symptoms suggestive of coronary heart disease.

The living probands, their spouses, and the closest relatives of the deceased probands were examined by the author. All first-degree relatives were listed, and consent was obtained to contact these and to obtain the death certificates from any deceased family members.

RELATIVES

The probands had 812 living and 517 deceased parents and sibs. The status of 42 relatives was unknown. The living relatives were sent a questionnaire on their medical history, and asked to report to local medical laboratories where resting 12-lead electrocardiograms were recorded (from relatives past age 40) and advice was available for filling out the questionnaire. The questionnaire and the recorded data were then forwarded to Helsinki University Hospital for analysis. The information requested was obtained from 721 (88·8%) of the living relatives.

The number of living and deceased participants in different study groups is shown in Table 1. Parents and sibs who had died before the age of 30 were not included in the study. The distribution of the birth dates of participating relatives was similar in all study groups (Fig. 1). The mean age for both the living sisters and brothers was 47·0 years.

Data from relatives

The questionnaires obtained from the relatives yielded information about previous diagnoses of cardiovascular diseases, and about present medication and health. The questionnaires were, in general, well completed; a few incomplete ones were amended by mail or telephone. To assess the reliability of the questionnaire data, a sample of 145 relatives was invited to have a clinical examination. Ninety-one per cent of them complied and were examined. The reporting of diagnosed coronary heart disease and of other cardiovascular diseases appeared to be reliable.

The reported diagnoses of coronary heart disease were standardised by checking them against the records of hospitals and private physicians. The diagnosis of past myocardial infarction was accepted only when the records reviewed disclosed unequivocal changes in the electrocardiogram or in serum enzyme pattern. Other cases of reported coronary heart disease (referred to here as 'other clinical coronary heart disease') were accepted only if the available data also described the basis of the diagnosis. The reported diagnosis of coronary heart disease could not be confirmed in 6 cases.

The electrocardiograms were coded by a trained technician using the Minnesota Code. Approximately every sixth recording was coded also by a second reader. The agreement between the two was good.

The causes of death of the deceased relatives were registered from death certificates, which were available for 95 per cent of the cases. To avoid the bias caused by changes in the nomenclature in earlier editions of ICD, the primary cause of death was recorded according to the latest (1965) revision of the classification in the Central Statistical Office of Finland. Approximately 75 per cent of the confirmed coronary heart disease deaths were so reported also by the relatives. Most errors in reporting were on the side of underreporting. In addition, all the available hospital records of the deceased sibs were reviewed. These records did not disclose coronary heart disease in any of the cases in which the primary cause of death was not coronary heart disease.

METHODS OF DATA ANALYSIS

Life tables

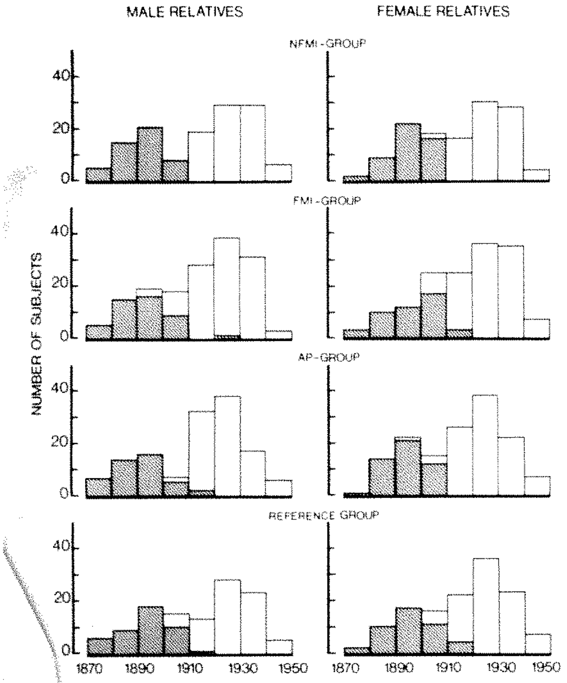
Life tables were obtained for the sibs, fathers, and mothers of the probands by the method of Cutler and Ederer (1958). The parents and sibs were entered on the tables at the age of 30, and they were withdrawn at the end of 1974 or at the age of death if they had died before that date. Life tables were constructed for mortality from all causes, from all cardiovascular diseases (ICD Nos. 400–450) and from coronary heart disease (410–414). A second type of life table was also constructed for combined morbidity and mortality from coronary heart disease. The occurrence of non-fatal coronary heart disease was made analogous to death from coronary heart disease, and the affected relatives were withdrawn at the age of their first coronary heart disease event, or at the age of death in the fatal cases in which the age of the first event was unknown.

The differences in the cumulative probabilities of

Table 1 *Number of participants in different study groups*

Study group	*Non-fatal myocardial infarction (NFMI)*		*Fatal myocardial infarction (FMI)*		*Angina pectoris (AP)*		*Reference*	
Number of probands	*50*		*55*		*53*		*53*	
Relatives	*Alive*	*Dead**	*Alive*	*Dead**	*Alive*	*Dead**	*Alive*	*Dead**
Fathers	2	47	1	49	4	49	5	46
Mothers	14	36	9	37	10	40	17	31
Brothers	69	16	78	36	81	16	65	16
Sisters	75	5	104	11	94	5	93	3
Total relatives	160	104	192	133	189	110	180	96

* Deceased who survived to age 30 are included.



1 *Distribution of deceased* (■) *and living* (□) *rticipants by year of birth.*

an event between two groups of relatives were tested according to Mantel (1966). The test evaluates the differences between the life table patterns in their entirety rather than at isolated points only.

For statistical testing of qualitative variables, the χ^2 test was used. The effect of multiple (non-independent) observations within a family was disregarded in all statistical tests of the study. Hence the significance tests described will have to be interpreted as rough measures of strength of association between the variables.

In the following text, the non-fatal myocardial infarction, fatal myocardial infarction, and angina pectoris groups will often be referred to jointly as case groups.

OCCURRENCE OF CORONARY HEART DISEASE AMONG RELATIVES

Parents

About 90 per cent of both case and reference fathers were deceased. One-third of case fathers and one-fifth of reference fathers had died of coronary heart disease ($P < 0{\cdot}05$). There were no appreciable differences in the total mortality nor in the mortality from specified causes between the fathers of the non-fatal myocardial infarction, fatal myocardial infarction, and angina pectoris probands.

Curves of the cumulative probabilities of dying from all causes, from all cardiovascular causes, and from coronary heart disease for all case fathers and reference fathers are presented in Fig. 2. The risk of fatal coronary heart disease was much higher for case fathers than for reference fathers.

By the age of 70, case fathers had a 36 per cent chance of dying from coronary heart disease, which denotes an approximately sixfold excess in cumulative risk over the risk of reference fathers ($P < 0{\cdot}01$). However, the difference in risk decreased with advancing age. Cerebrovascular deaths were also slightly more common among case than reference fathers, whereas mortality from other causes was slightly lower in case group than in reference group. The slightly higher overall mortality of case fathers could thus be totally attributed to the increased rate of cardiovascular disease.

The cumulative risk of dying before the age of 70 for case mothers was 2·0 times greater for case than for reference mothers ($P < 0{\cdot}05$) (Fig. 3). At later

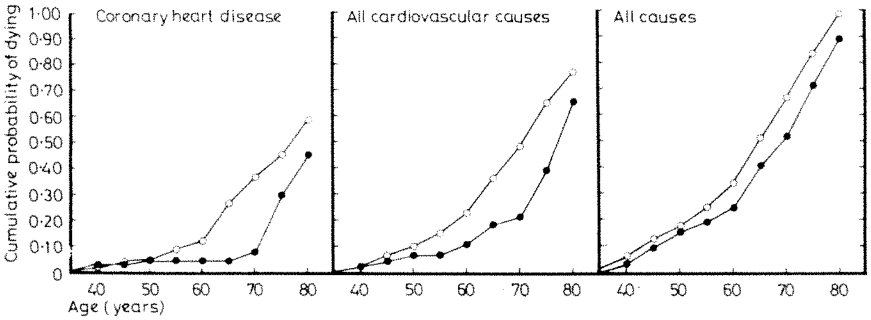


Fig. 2 *Cumulative probability of case* (——○——) *and reference* (——●——) *fathers of dying from coronary heart disease (International Classification of Diseases Code Nos. 410-414), from all cardiovascular causes (400-450), and from all causes.*

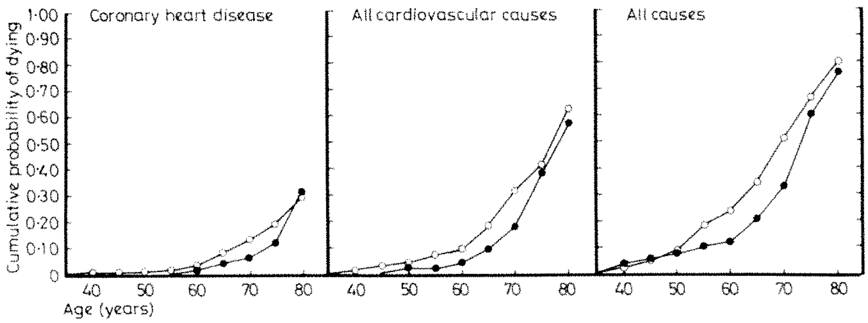


Fig. 3 *Cumulative probability of case (——○——) and reference (——●——) mothers of dying from coronary heart disease, all cardiovascular causes, and from all causes.*

ages, the difference in risk was not apparent. The increased risk of case mothers was mostly, but not totally, attributable to cardiovascular disease. The mortality of mothers of the non-fatal myocardial infarction, fatal myocardial infarction, and angina pectoris probands was similar.

Brothers

Approximately one-third of the brothers of the non-fatal myocardial infarction, fatal myocardial infarction, and angina pectoris probands had developed fatal or non-fatal coronary heart disease (Table 2). The frequencies are 3·5 times greater than for reference brothers ($P < 0·001$).

Curves of the cumulative probabilities of developing coronary heart disease for case and reference brothers are shown in Fig. 4. The risk of coronary heart disease for case brothers was 44 per cent by the age of 55, and increased to 70 per cent by the age of 65; the cumulative risk of coronary heart disease by this age was 4·5 times greater for case brothers than for reference brothers ($P < 0·001$).

There were some differences between the clinical manifestations of coronary heart disease in the various case groups. Among the brothers of the probands who had suffered fatal myocardial infarction, cardiac deaths predominated, whereas the brothers of the non-fatal myocardial infarction and angina pectoris probands tended to develop mostly non-fatal forms of coronary heart disease (Table 3).

Sisters

Coronary heart disease had been diagnosed in approximately 12 per cent of the sisters of the affected probands, which is twice as frequently as in reference sisters ($P = 0·09$) (Table 4). The probability of developing fatal or non-fatal coronary heart disease for case sisters was 20 per cent by age 55. The risk doubled within the next decade, [illegible] by age 65 there was a 2·6-fold excess in cumulative risk of coronary heart disease for case sisters over that for reference sisters ($P < 0·05$) (Fig. 4). As also noticed among the brothers, coronary heart disease was often fatal among the sisters of the fatal myocardial infarction probands, whereas other clinical forms of coronary heart disease prevailed in the other groups (Table 3).

Electrocardiographic abnormalities

Ischaemic electrocardiographic abnormalities, defined as Minnesota Code Nos. 1.1–3, 4.1–3, 5.1–2, were significantly more common among case sibs than among reference sibs (16·4% vs. 7·4%, $P < 0·01$) (Table 5). Furthermore, electrocardio-

Table 2 *Frequency of clinical coronary heart disease in brothers*

Study group	*Number of brothers*	*Number of cases with clinical coronary heart disease*					
		Fatal myocardial infarction	*Non-fatal myocardial infarction*	*Other forms of coronary heart disease*	*All coronary heart disease*	*(%)*	*Risk ratio*
NFMI	85	10	4	11	25	(29·4)	3·0
FMI	114	19	10	15	44	(38·6)	3·9
AP	97	8	9	18	35	(36·1)	3·6
All case	296	37	23	44	104*	(35·1)	3·5
Reference	81	1	2	5	8	(9·9)	1·0

* $P < 0·001$ for the difference between all case groups and reference group.

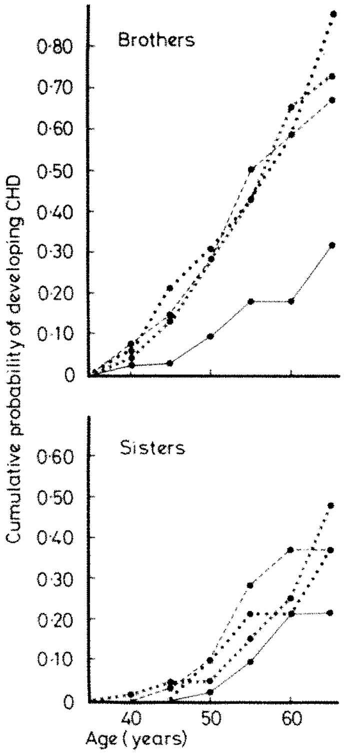


Fig. 4 *Cumulative probability of developing fatal or non-fatal coronary heart disease of the sibs of the non-fatal myocardial infarction*—(xxx), *fatal myocardial infarction*—(●●●), *angina pectoris*—(----), *and reference* (———) *probands.*

Table 3 *Cumulative probability of fatal coronary heart disease for sibs before age 60 (%)*

Study group	*Fatal myocardial infarction*	*Non-fatal myocardial infarction*	*Angina pectoris*	*Reference*
Brothers	34·5*	28·9*	15·4†	4·4
Sisters	8·2	3·5	—	—

* $P < 0{\cdot}01$ for the difference between fatal myocardial infarction/non-fatal myocardial infarction group and reference group.
† $P < 0{\cdot}05$ for the difference between angina pectoris group and reference group.

graphic abnormalities were more common among the sibs of the angina pectoris probands than among other case sibs (22·9% vs. 12·9%, $P < 0{\cdot}01$). The increased prevalence of ischaemia was noted also among those sibs of the angina pectoris probands who were free of clinical coronary heart disease.

Signs of probable old myocardial infarction (Minnesota Code Nos. 1.1, 1.2+5.1 or 1.2+5.2) were present in 5·0 per cent of the electrocardiographic tracings of case brothers. In only 2 brothers had the myocardial infarction been clinically silent. Signs of old myocardial infarction were present in the electrocardiograms of 1·4 per cent of case sisters. None of the myocardial infarctions in women had gone clinically undetected.

RELATION OF PARENTAL HISTORY TO CORONARY HEART DISEASE IN THE FAMILY

There were 14 case families in which the mother had died of coronary heart disease before age 70. The risk of coronary heart disease was exceptionally great for the offspring of these mothers (Table 6). By age 55, the risk for their daughters was 41 per cent, 3 times greater than that for the remaining case sisters ($P < 0{\cdot}01$), and for their sons (other than probands) the risk was 63 per cent, which denotes a twofold increase over the risk for the remaining case brothers ($P < 0{\cdot}05$).

Thirty-eight case fathers had died of coronary heart disease before the age of 70. The risk of coronary heart disease was slightly increased for the offspring of these fathers, when compared with the risk for the offspring of case families without any parental history of premature coronary heart disease (Table 6). The risk appeared to be more distinctly increased for the offspring of fathers who died of coronary heart disease before the age of 60,

Table 4 *Frequency of clinical coronary heart disease in sisters*

Study group	*Number of sisters*	*Number of cases with clinical coronary heart disease*					
		Fatal myocardial infarction	*Non-fatal myocardial infarction*	*Other forms of coronary heart disease*	*All coronary heart disease*	*(%)*	*Risk ratio*
NFMI	80	2	3	4	9	(11·3)	1·8
FMI	115	3	2	7	12	(10·4)	1·7
AP	99	—	4	11	15	(15·2)	2·4
All case	294	5	9	22	36*	(12·2)	2·0
Reference	96	—	—	6	6	(6·3)	1·0

* $P > 0{\cdot}05$ for the difference between all case groups and reference group.

Table 5 *Frequency of ischaemic changes* (%) in resting electrocardiograms of sibs over age 40*

Study group	*Brothers*		*Sisters*	
	All	*Without clinical coronary heart disease*	*All*	*Without clinical coronary heart disease*
Non-fatal myocardial infarction	8·5	5·6	14·5	9·1
Fatal myocardial infarction	19·6	9·1	9·3	6·1
Angina pectoris	22·0†	9·1	23·6†	14·0
Reference	5·7	4·3	8·8	4·8

* Minnesota Code 1.1–3, 4.1–3, 5.1–2.

† $P < 0·01$ for the difference between the sibs of AP-group and reference group.

but the number of subjects at risk was too small to warrant any firm conclusions.

The risk of coronary heart disease was similar for the offspring of families with a parental history of coronary heart disease past the age of 70 and for the offspring of families without any parental history of coronary heart disease. However, when both parents had died of coronary heart disease at a later age, there appeared to be a slight increase in the risk of coronary heart disease for the offspring.

There were 5 reference families with a history of fatal coronary heart disease before the age of 70 in one of the parents. One-half of the cases of coronary heart disease among reference sibs came from these families. This denotes an eightfold increase in the risk of coronary heart disease for the offspring of the affected reference parents, compared with the risk for the offspring of non-affected parents.

FAMILY CLUSTERING OF CORONARY HEART DISEASE

Distinct familial clustering of coronary heart disease was present in one-third of case families (Table 7). These families had a minimum of 3 members affected by coronary heart disease, accounting for two-thirds of the total cases of coronary heart disease in the case group. Impressive clustering of coronary heart disease was not confined to the families with a history of early coronary death in parent. There were 3 to 7 affected sibs in 1[illegible] families in which neither parent had died of coronary heart disease before the age of 70.

Table 6 *Cumulative probability of developing coronary heart disease by age 55 (%) for case sibs according to parental coronary heart disease*

	Brothers	*Sisters*
Mother died of coronary heart disease before age 70	63·3*	41·4†
Father died of coronary heart disease before age 70	42·7	28·9
Neither parent died of coronary heart disease before age 70	40·2	14·6

* $P < 0·05$ for the difference between the brothers with a maternal coronary heart disease history and of brothers without parental history of coronary heart disease.

† $P < 0·01$ for the difference between the sisters with a maternal history of coronary heart disease and of sisters without parental history of coronary heart disease.

Discussion

In the present study, a major effort was made to avoid the biases common to family studies of coronary heart disease (Haenszel, 1950; Epstein, 1964; Murphy, 1967; Napier *et al.*, 1972). No hearsay evidence of coronary heart disease was accepted. All information was collected directly from the relatives, verified by medical records, and reviewed in a standardised way to exclude the diagnoses established by intuition or family history only. By these means, most false positive diagnoses were likely to be eliminated, but also some real cases of coronary heart disease may have been missed. Furthermore, the selection of probands in the present study was not restricted to patients in hospital. The myocardial infarction probands were the consecutive incidence cases of myocardial infarction within whole communities. The selection of the angina pectoris probands was by necessity, however, more restricted. Only a small, perhaps the most severe (Frank *et al.*, 1973), fraction of clinical angina pectoris could be included; incidence cases of angina most probably would include, along with true angina, such heterogeneous conditions as pre-infarction angina and early stages of other, even non-cardiac, diseases. Nevertheless, the angina pectoris probands were selected by uniform criteria from a group that is fairly representative of the male

Table 7 *Distribution of cases of coronary heart disease in families (proband excluded)*

Study group	*Non-fatal myocardial infarction*	*Fatal myocardial infarction*	*Angina pectoris*	*Reference*
Number of families	*50*	*55*	*53*	*53*
Number of family members with coronary heart disease	%	%	%	%
0	34·0	20·0	24·5	52·8
1	28·0	41·8	41·5	32·1
2	28·0	16·4	18·9	11·3
3	4·0	12·7	7·5	3·8
4 or more	6·0	9·1	7·5	—

$P < 0·01$ between non-fatal myocardial infarction/fatal myocardial infarction/angina pectoris families and reference families.

population in the industrialised communities of the study. Likewise, though not selected from the population at large, the reference probands were fairly representative of men of their age in the study communities. Even if somewhat better health than that found in the general population could be expected in this group of mostly employed men, free of any symptoms of coronary heart disease (McMichael *et al.*, 1975), the morbidity and mortality of the relatives of these probands appeared to be very similar to that of the general population in Finland, if judged from the preliminary data available from a population study of 50 000 Finns (A. Aromaa, unpublished results).

In the present study, the degree of familial aggregation of coronary heart disease appeared to be similar in the non-fatal myocardial infarction, fatal myocardial infarction, and angina pectoris groups. However, distinct differences between the groups were found as to the predominant clinical manifestation of the disease. While fatal coronary heart disease predominated among the sibs in the fatal myocardial infarction group, non-fatal coronary heart disease was most common among the sibs of the angina pectoris probands. Furthermore, the frequency of ischaemic electrocardiographic abnormalities without clinical coronary heart disease, which perhaps is equivalent to preclinical disease, was highest in this group. Similar familial resemblance in the clinical manifestations of coronary heart disease as observed here was found also in an area of Finland with a lower incidence of coronary heart disease (unpublished observations). These observations suggest that familially determined differences may exist in the atherosclerotic process underlying the various clinical manifestations of coronary heart disease. Alternatively, the trigger mechanisms behind the various clinical manifestations of coronary heart disease may be familially determined.

The degree of familial aggregation of coronary heart disease observed in this study is similar to that of most other studies. An excess mortality from coronary heart disease among case fathers, especially among fathers of young probands, has been reported before (Shanoff *et al.*, 1961; Rose, 1964; Slack and Evans, 1966; Deutscher *et al.*, 1970; Friedman *et al.*, 1974; Phillips *et al.*, 1974). The lack of aggregation of coronary heart disease in mother-sib pairs also agrees with most earlier reports (Gertler and White, 1954; Thomas and Cohen, 1955; Phillips *et al.*, 1974). The possibility of modest excess mortality of mothers from coronary heart disease or from cerebrovascular diseases found by others (Shanoff *et al.*, 1961; Rose, 1964; Friedman *et al.*, 1974) cannot be totally excluded, however. Part of the higher total mortality of case mothers might have been the result of cardiovascular causes despite divergent diagnoses in the death certificates. It is also possible that latent cardiovascular disease may have increased the susceptibility to death from other causes and coronary heart disease perhaps would have become evident at a later age, if death from other causes had not intervened. A somewhat increased mortality from coronary heart disease could, in fact, be shown for the mothers of the very youngest case probands (Rissanen, 1979). The three- to four fold excess in the rate of coronary heart disease among case sibs observed in this study also agrees with their investigations which have reported two- to tenfold increases in the rate of coronary heart disease among the brothers and two- to fourfold increases among the sisters of affected men (Gertler and White, 1954; Thomas and Cohen, 1955; Russek and Zohman, 1958; Shanoff *et al.*, 1961; Rose, 1964; Slack and Evans, 1966; Phillips *et al.*, 1974).

From the above it appears that the excess rate of coronary heart disease in case relatives over that of reference relatives shown here is no greater than in studies from other countries. It should be remembered, however, that the frequencies of coronary heart disease in both case and reference relatives in the present study are remarkably higher than those reported elsewhere. For instance, the risk of coronary heart disease for case brothers in the present study was greater than that for the affected brothers in families with type II familial hypercholesterolaemia in a report from the United States (Stone *et al.*, 1974). As another example, mortality from coronary heart disease of reference fathers of the present study was approximately 5 times greater than that of the fathers of young Hawaiian-Japanese men suffering from coronary heart disease (Phillips *et al.*, 1974).

The relatively modest excess occurrence of coronary heart disease in case relatives over that in reference relatives could be taken to suggest that familial factors play only a minor role in the causation of coronary heart disease. However, even this modest excess may indicate a substantial familial element in the disease of the present study cohort. No multifold excess of familial aggregation should be expected against such a high rate of coronary heart disease as was found in reference relatives. Furthermore, an appreciable proportion of the high rate of coronary heart disease among reference relatives was also attributable to family aggregates of the disease. Almost one-half of the reference sibs affected by coronary heart disease originated from the 5 families in which 1 of the parents had died of coronary heart disease before the age of 70.

Aggregation of coronary heart disease was most distinct in case families in which the mother had died of coronary heart disease at a relatively young age. Approximately one-half of the children of such mothers, whether daughters or sons, had developed coronary heart disease early in life. It appears likely that these mothers possessed and passed to their offspring sets of highly atherogenic genes that were strong enough to outweigh the natural resistance of females to coronary heart disease. Similar clustering of coronary heart disease in families of affected mothers as shown here has been observed previously by Slack and Evans (1966). They suggested also that the genetic component may be more prominent in coronary heart disease in women than in men. This is supported by the present findings.

Since the frequency of coronary heart disease in case families with a paternal history of coronary heart disease before the age of 70 was considerably lower than that in the families with a maternal history, the factors involved in the transmission of susceptibility to coronary heart disease through the paternal line of descent appear less potent and may be qualitatively different from the factors involved in the transmission of disease susceptibility through the maternal line of descent.

Parental history of coronary heart disease was not a prerequisite for a distinct familial aggregation of coronary heart disease. Multiple sibs were affected in several families without any parental history of the disease. It may be argued that the diagnosis of coronary heart disease in a parent was missed in such families. In most of them, however, the parents could be shown to have survived to an old age and to have died of non-cardiac causes. For instance, in the family with the strongest clustering of coronary heart disease, with 7 out of 9 sibs affected at ages 30 to 59, both parents had enjoyed good health to an old age and succumbed from causes other than coronary heart disease.

The failure to show parent-offspring concordance for coronary heart disease does not exclude the possibility that inherited factors would be important causes of the aggregation of the disease in the offspring. It is possible that the parents were carriers of atherogenic genes which did not become fully expressed until enhanced by an exposure to additional atherogenic factors arising from the changing environment. Such factors are likely to be responsible for the increase observed in the rate of coronary heart disease in the offspring generation.

This increase was modest, however, when compared with the pronounced secular increase in the rate of coronary heart disease which is well documented in the general population. Environmental influences thus do not appear to be major determinants of the development of the disease in case subjects. This impression is substantiated by the fact that in many of the sibships with multiple cases of coronary heart disease, distinctly similar disease histories—both as to the age of onset and the clinical form of the disease—were found in sibs with widely different environments and life styles. For instance, 2 brothers, 1 a resident of Finland and the other of New Zealand for the last 45 years, developed angina at ages 50 and 51, respectively. Such similarities are likely to arise from shared genetic background.

In some families, especially in a majority of those with a maternal history of coronary heart disease, the number affected by coronary heart disease was high enough to suggest the effect of dominant gene(s), directly causing coronary heart disease. In most families, however, the genetic factors involved are likely to be polygenic. The relatively modest overall aggregation of coronary heart disease among case relatives if compared with reference relatives, as well as the decline in risk of coronary heart disease between case and reference relatives with advancing age, suggest an interplay of multiple factors in the development of this complex disease (Carter, 1969).

The results of the study call attention to the role of family history of coronary heart disease in predicting the future victims of the disease. Screening for parental history of coronary heart disease before the age of 70 would have identified one-third of case probands, most of them with multiple affected sibs, decades before the emergence of the clinical disease. By the same procedure, only 9 per cent of healthy reference men would have been identified. The high rate in the sibs of these men shows that these reference families were in greatest need of preventive action. Admittedly, screening for parental history of coronary heart disease would have been a relatively insensitive test, failing to identify a majority of the future cases of the disease. It is doubtful, however, whether any other single measure would have had a better predictive power in this population with such a high overall risk of coronary heart disease. The sensitivity of screening by family history could have been improved considerably had the history of premature coronary heart disease in a sib also been taken into account. By so doing, two-thirds of the case probands could have been identified before the onset of the clinical disease.

Therefore, at least in Finland, family history of coronary heart disease should be recognised as a major risk factor, which is well suited, and should also be used as a simple screening test for coronary prone individuals.

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Mechanisms of prolongation of pre-ejection period in patients with left ventricular disease

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SUMMARY In order to determine the mechanism underlying prolongation of the pre-ejection period in patients with left ventricular disease, 11 patients with congestive cardiomyopathy and 29 with coronary artery disease, 10 of whom were taking beta-adrenergic blocking drugs, were studied non-invasively. Recordings of carotid pulse, and apex, phono-, and echocardiogram were obtained. In the absence of treatment with beta-blocking drugs, prolongation of pre-ejection period correlated closely with incoordinate left ventricular wall movement during isovolumic contraction assessed from simultaneous apex and echocardiograms. There was no correlation between pre-ejection period index (PEPI) and end-diastolic dimension and PEPI correlated poorly with fractional shortening and peak Vcf. A PEPI of greater than 140 ms was associated with incoordinate contraction in all but one case, and of less than 140 ms with normal contraction in all. Therapeutic doses of beta-blocking drugs caused prolongation of PEPI to a greater extent than would have been predicted from wall movement during isovolumic contraction. Incoordinate left ventricular contraction and a negative inotropic effect both therefore prolong PEPI, but by different mechanisms, whose effects can be separated in individua patients using non-invasive methods based on echocardiography.

Prolongation of pre-ejection period is commonly used to detect the presence of left ventricular disease, though the mechanism of this prolongation of pre-ejection period is obscure. A reduction in 'contractility' is frequently invoked, but this term is not adequately defined, and means little more than the presence of clinical evidence of left ventricular disease. We have, therefore, measured pre-ejection period and other systolic time intervals in patients with ischaemic heart disease or cardiomyopathy, analysing any impairment of left ventricular function at rest in terms of abnormal cavity size, incoordinate contraction, and reduced peak systolic rate of wall movement, measured echocardiographically. These observations were compared with those made during chronic administration of beta-blocking drugs in therapeutic dosage.

Methods

Systolic time intervals were measured and echocardiographic examinations were performed in 40 patients, who were divided into the following groups:

Group 1 : 11 patients with congestive cardiomyopathy. This diagnosis was made by echocardiography in patients without a history of chest pain or electrocardiographic evidence of infarction, in whom cavity size was increased and the amplitude wall movement reduced. Since we no longer perform cardiac catheterisation in such patients, this group may have included individuals with advanced ischaemic heart disease. This limitation was accepted, since the pathological process underlying the left ventricular disease was of no importance to the design of the study.

Group 2 : 19 patients with coronary artery disease, confirmed by coronary arteriography. None of these patients had taken any beta-adrenergic blocking drug within 2 weeks of the study.

Group 3 : 10 patients with coronary artery disease, again confirmed by coronary arteriography, who were on maintenance treatment with beta-blocking drugs, either propranolol, oxprenolol, or atenolol. In each case, the dose had been adjusted to give maximum therapeutic effect.

Patients with left bundle-branch block, atrial fibrillation, systemic hypertension, or valvar heart disease were excluded from the study. Treatment with digitalis preparations and diuretics was not interrupted.

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SYSTOLIC TIME INTERVALS

Systolic time intervals were derived from simultaneous recordings of phonocardiogram, carotid pulse, and electrocardiogram, made with the patient supine, after a period of approximately 15 minutes rest. The output was displayed on a Cambridge Instruments strip-chart photographic recorder, operating at a paper speed of 100 mm/s. The electrocardiogram recorded was usually lead II, but occasionally other leads were used when these showed the onset of electrical depolarisation more clearly. Phonocardiograms were recorded from the site where the aortic component of the second sound was heard most easily, using a Cambridge (Leatham) microphone and a high-frequency filter. The pulse tracing was taken from the right carotid artery, using a Cambridge Instruments transducer, with a time constant of 4 s, and a lower frequency limit of 0·05 Hz. The following intervals were measured.

(1) Total electromechanical systole ($Q\text{-}S_2$): this was measured from the onset of left ventricular depolarisation to the start of the first high-frequency vibration of the aortic component of the second heart sound.

(2) Left ventricular ejection time (LVET): this was measured from the onset of the rapid upstroke of the carotid pulse to the trough of the incisura.

(3) Pre-ejection period (PEP): this was derived by subtracting left ventricular ejection time from $Q\text{-}S_2$ interval. All intervals were measured to the nearest 5 ms from 10 successive beats, and average values obtained. Using regression equations derived by Weissler *et al.* (1969b), the pre-ejection period index (PEPI) was calculated. In addition, values of the ratio PEP/LVET were also derived.

ECHOCARDIOGRAPHIC MEASUREMENTS

These recordings were made immediately before those made for measurement of the systolic time intervals. Echocardiograms were obtained with either a Cambridge Instruments or a Smith-Kline Ekoline 20 Ultrasonoscope (frequency 2·25 MHz, repetition rate 1000/s). The output was displayed on a Cambridge Instruments strip chart recorder, at a paper speed of 100 mm/s. The patients lay 30 degrees on their left side and the transducer was directed to measure the left ventricular dimension, from the left side of the septum to the endocardial surface of the posterior wall at the level of the tips of the mitral valve leaflets. All echocardiograms showed clear, continuous endocardial echoes so that they could be digitised. A simultaneous electrocardiogram and apex cardiogram were also recorded, the latter from the point of maximum impulse, using the same transducer as that used for the carotid pulse.

Echocardiograms and apex cardiograms were digitised as previously described (Venco *et al.*, 1977). Plots were made of the original digitised data, left ventricular dimension and its first derivative with respect to time, normalised rate of change of dimension (VCF) and, finally, the time relations between left ventricular dimension and apex cardiogram, displayed as a loop. At least 3 beats were digitised from each record, and mean values were taken. From these plots, the following measurements were made:

(1) End-diastolic (EDD) and end-systolic (ESD) dimensions.

(2) Fractional shortening, derived as (EDD − ESD)/EDD.

(3) Peak rate of reduction of normalised dimension during ejection (peak Vcf).

(4) The change in left ventricular dimension during the time of inscription of the upstroke of the apex cardiogram, between its onset and the 'E' point (isovolumic contraction), expressed as a percentage of the total dimension change during the cardiac cycle.

STATISTICAL METHODS

In patients of groups 1 and 2, PEPI was correlated with EDD, fractional shortening, peak Vcf, and percentage reduction in left ventricular dimension during isovolumic contraction. Multiple regression analysis was also performed to assess the relative associations between PEP or PEP/LVET and EDD, fractional shortening, peak Vcf, and dimension change during the upstroke of the apex cardiogram.

Results

The systolic time intervals and echocardiographic measurements in the 3 groups of patients are given in detail in Table 1.

In groups 1 and 2, PEPI was found to correlate most strongly with left ventricular dimension change during the upstroke of the apex cardiogram ($r = 0{\cdot}76$, $P < 0{\cdot}001$). There was no significant correlation with end-diastolic dimension ($r = 0{\cdot}22$, NS) and correlation was poor with fractional shortening ($r = 0{\cdot}39$, $P < 0{\cdot}5$) and peak Vcf ($r = 0{\cdot}42$, $P < 0{\cdot}05$). The relation between PEPI and dimension change during the upstroke of the apex cardiogram is shown in Fig. 1. Of 10 patients with PEPI less than 140 ms, all had a left ventricular dimension change less than 15 per cent, the upper limit of normal (Venco *et al.*, 1977), while 19 of the remaining 20 had a left ventricular dimension change greater than 15 per cent. This relation is very significant statistically (Fisher's exact probability test, $P < 0{\cdot}0001$).

The PEP/LVET ratio in groups 1 and 2 also correlated best with left ventricular dimension change during the upstroke of the apex cardiogram ($r = 0{\cdot}77$, $P < 0{\cdot}001$), but also, to a lesser extent, with fractional shortening ($r = -0{\cdot}53$, $P < 0{\cdot}002$) and peak Vcf ($r = -0{\cdot}49$, $P < 0{\cdot}01$). There was no significant correlation with end-diastolic dimension. Multiple correlation on PEP/LVET, peak Vcf, and left ventricular dimension change resulted in the following regression equation:

$$\text{PEP/LVET} = 0{\cdot}35 - 0{\cdot}038 \text{ peak Vcf} + 0{\cdot}0084 \text{ (dimension change).}$$

The multiple correlation coefficient was 0·79. In addition, peak Vcf and fractional shortening were themselves significantly correlated ($r = 0{\cdot}90$), and so could not be treated as independent variables.

Table 1 *Systolic time intervals and echocardiographic measurements in patients with congestive cardiomyopathy and coronary artery disease*

Case no.	*PEPI (ms)*	*PEP/ LVET*	*EDD (cm)*	$\frac{EDD - ESD}{EDD}$	*Peak Vcf* (s^{-1})	*DMUP (%)*
Group 1 Congestive cardiomyopathy						
1	117	0·29	7·2	0·11	0·65	15
2	164	0·58	6·2	0·14	0·82	21
3	157	0·59	6·5	0·10	0·80	25
4	164	0·57	6·2	0·095	1·4	28
5	162	0·56	6·9	0·12	0·85	30
6	143	0·45	5·7	0·35	2·2	25
7	155	0·65	6·3	0·16	1·4	28
8	171	0·67	5·7	0·16	1·1	29
9	153	0·61	6·8	0·15	1·1	36
10	124	0·37	8·2	0·15	1·3	5
11	141	0·54	6·2	0·12	1·0	28
12	155	0·52	8·2	0·24	1·5	28
Group 2: Coronary artery disease not on beta-blocker						
13	115	0·33	6·3	0·20	1·5	10
14	124	0·42	3·7	0·14	2·0	14
15	129	0·32	4·3	0·44	2·8	12
16	151	0·60	4·0	0·11	1·1	34
17	168	0·71	5·4	0·22	1·7	19
18	116	0·29	4·7	0·39	2·5	10
19	168	0·51	5·7	0·28	1·6	27
20	167	0·58	6·8	0·17	1·2	34
21	155	0·57	5·2	0·33	2·5	37
22	138	0·43	4·9	0·20	1·9	14
23	154	0·46	4·8	0·21	1·2	28
24	147	0·47	5·8	0·17	1·5	21
25	145	0·39	3·9	0·18	1·4	12
26	95	0·22	4·7	0·34	2·4	7
27	128	0·33	4·0	0·36	2·4	9
28	165	0·51	4·5	0·22	1·9	37
29	149	0·53	7·5	0·080	0·45	40
30	128	0·34	4·2	0·40	2·3	8
Group 3 Coronary artery disease on beta-blocker						
31	147	0·44	4·8	0·17	1·3	34
32	146	0·43	5·5	0·18	0·80	15
33	198	0·69	6·5	0·10	0·90	31
34	169	0·53	5·4	0·18	1·3	11
35	147	0·42	4·7	0·23	1·9	3
36	154	0·48	4·5	0·084	1·0	22
37	133	0·35	5·4	0·34	2·3	10
38	129	0·36	5·8	0·39	2·0	11
39	167	0·50	6·0	0·22	1·4	23
40	148	0·39	5·1	0·39	1·4	15

PEPI, pre-ejection period index; LVET, left ventricular ejection time; EDD, end-diastolic dimension; ESD, end-systolic dimension; Vcf, velocity of circumferential fibre shortening; DMUP, dimension change during upstroke of apex cardiogram.

In group 3 patients, who were taking therapeutic doses of beta-blocking drugs, values of PEPI were greater than would have been predicted from dimension change during isovolumic contraction in 9 out of 10 patients (Fig. 2).

Discussion

There is much evidence to suggest that the pre-ejection period is prolonged by the presence of left ventricular disease. This has been reviewed in detail by Harris (1974), and shown to be true not only for primary myocardial disease (Spodick *et al.*, 1972; Armstrong *et al.*, 1973), but also for the myocardial disease occurring in hypertension (Tarazi *et al.*, 1969), valvar heart disease, or coronary artery disease (Jezek, 1963; Pouget *et al.*, 1971; Meng *et al.*, 1976). However, analysis of the underlying disturbance has been limited by difficulties in the definition of myocardial contractility. This has been defined in terms of the findings of experiments on isolated heart muscle, whose theoretical basis now appears dubious, and

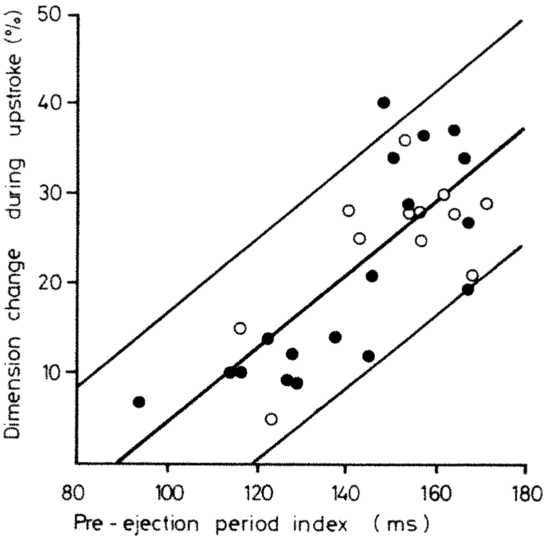

Fig. 1 *Relation between prolongation of pre-ejection period and abnormal left ventricular dimension change during upstroke of apex cardiogram in patients with coronary artery disease* (○) *or congestive cardiomyopathy* (●).

whose extrapolation to patients with cardiac disease unsatisfactory. In the present study, therefore, we have avoided these ideas, and instead attempted to describe clinical left ventricular disease in terms of (1) abnormal cavity size, (2) reduced rates of left ventricular wall movement, and (3) contraction pattern. These variables can readily be measured by non-invasive techniques based on echocardiography which have been validated in our laboratory against invasive methods. Estimates of transverse left ventricular diameter at the level of the mitral valve can be made by echocardiography, and agree with those derived from angiocardiograms (Gibson, 1973). At end-diastole, these are little affected by an incoordinate left ventricular contraction pattern (Ludbrook *et al.*, 1973). Measurement of peak Vcf has also been validated against angiocardiography, and in patients with a co-ordinate contraction pattern and competent mitral valve it has been shown to correlate closely with peak left ventricular dP/dt (Gibson and Brown, 1975a, 1976). Finally, abnormal changes in left ventricular dimension during the time of inscription of the upstroke of the apex cardiogram between the onset and the 'E' point correlate closely with regional disturbances of wall movement during early systole, shown angiographically (Doran *et al.*, 1978), independent of other abnormalities of left ventricular wall movement that may be present.

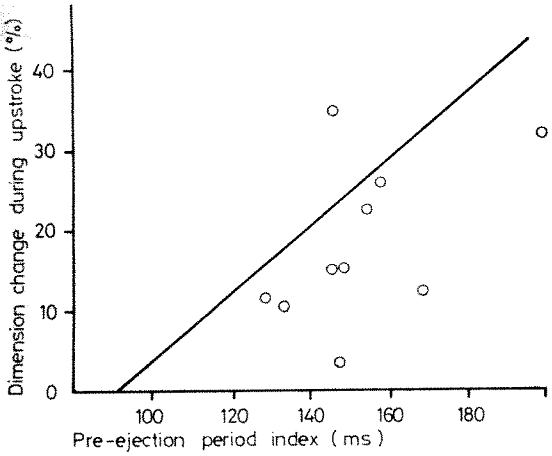

Fig. 2 *Effect of therapeutic doses of beta-adrenergic blocking drugs on relation between pre-ejection period and abnormal dimension changes during isovolumic contraction. The regression line is derived from data of Fig. 1.*

The present results show clearly that prolongation of pre-ejection period is associated with abnormal dimension changes during the upstroke of the apex cardiogram, but not with either an increased transverse cavity dimension or a reduced peak Vcf. It might be objected that some of these measurements of cavity size or peak Vcf were obtained in patients with incoordinate wall movement and are, therefore, not representative of the behaviour of the left ventricle as a whole. However, they are clearly abnormal, whether or not they are representative, and so should have been associated with values of PEPI outside the normal range, if they were indeed the basis of the prolongation of pre-ejection period seen in patients with heart disease. Secondly, when the subgroup of patients was considered in whom apex cardiogram dimension relations were normal and thus in whom contraction patterns would be expected to be more uniform, the same lack of correlation was found. Thus normal values of PEPI were seen in association with cavity dimensions of up to 8·2 cm, fractional shortening as low as 0·15, or a peak Vcf of 0·65 s^{-1}.

A second limitation of the study is that dimension changes during the upstroke of the apex cardiogram have been shown to be sensitive and specific in detecting, but not necessarily in quantifying, the degree of incoordinate contraction judged angiographically. It is probably more appropriate, therefore, to use this method simply to categorise early systolic wall movement in individual patients as either normal or abnormal. When groups 1 and 2 patients were divided in this way, there was virtually no overlap between the two (Table 2). Nevertheless, the relation between the percentage dimension change during isovolumic contraction and prolongation of PEPI (Fig. 1) suggests that these measurements may, in fact, be regarded as semi-quantitative. We therefore conclude that prolongation of pre-ejection period in untreated patients with coronary artery disease or cardiomyopathy is the

Table 2 *Relation between PEPI and reduction in LV dimension during period of inscription of upstroke of apex cardiogram and coronary artery disease not receiving β-blockers.*

	Reduction in LV dimension during period of inscription of upstroke of apex cardiogram < 15%	*Reduction in LV dimension during period of inscription of upstroke of apex cardiogram* > 15%
PEPI < 140 ms	10	0
PEPI > 140 ms	1	19

Fisher exact probability test, $P < 0{\cdot}0001$.

result of asynchronous onset of contraction rather than slow contraction or abnormal cavity size.

The occurrence of abnormal wall movement early in systole has been recognised in patients with coronary artery disease for some years, and was described in detail by Karliner *et al.* (1971) and, more recently, by Gibson *et al.* (1978), using techniques for displaying regional left ventricular wall movement so that such abnormalities of timing could be easily appreciated. Left ventricular contraction patterns in patients with congestive cardiomyopathy were described by Kreulen *et al.* (1973), who noted that in approximately 50 per cent there was angiocardiographic evidence of incoordinate movement. In all these patients, the method of angiographic analysis is of importance. Although the most obvious abnormalities seen on direct inspection of the cine film are those of regional amplitude of wall movement, these areas do not necessarily show disturbed movement in early systole. Conversely, regions behaving abnormally in early systole frequently undergo a normal amplitude of movement later in ejection, though their timing may be delayed compared to the remainder of the ventricle (Gibson *et al.*, 1978). It has previously been shown that abnormal dimension changes during the upstroke of the apex cardiogram correlate specifically with those shown angiographically to occur in early systole, and are unrelated to regional reduction in amplitude (Doran *et al.*, 1978). Prolongation of pre-ejection period in our patients, therefore, is also likely to have been related specifically to these early systolic regional abnormalities of wall movement. This correlation would not have been detected unless the methods used had been based on a technique of angiographic analysis capable of distinguishing these disturbances of timing from the more commonly recognised ones of amplitude.

If activation is normal, then pre-ejection period depends on end-diastolic aortic and left ventricular pressures and the rate of rise of the left ventricular pressure pulse. Since hypertensive patients were not studied, and since left atrial pressure is likely to have been high rather than low in the presence of left ventricular disease, prolonged pre-ejection period in our patients was the result of reduced rate of left ventricular pressure rise. Such a reduction in peak left ventricular dP/dt has been shown in dogs by Rushmer (1956) by inducing incoordinate contraction using ventricular pacing. These observations were confirmed in man by Gibson and Brown (1975b), who showed that reduction in peak dP/dt correlated with the distortion of the left ventricular pressure dimension loop. The present results are compatible with these findings, and suggest that incoordinate left ventricular contaction during early systole causes the appearance of disturbed time relations between changes in dimension and the apex cardiogram, and also prolongs pre-ejection period by reducing the rate of rise of left ventricular pressure, thus explaining the statistical association between the two.

Pre-ejection period is also prolonged by propranolol in normal subjects and patients with heart disease (Harris *et al.*, 1967; Hunt *et al.*, 1970). This finding was confirmed in the present study, where it was also apparent that it was not associated with the expected degree of dimension change early in systole, suggesting that the mechanism by which it was brought about was different from that associated with heart disease. Though there is some evidence that propranolol administration may aggravate abnormalities of wall movement in patients with ischaemic heart disease (Helfant *et al.*, 1971), other studies have shown either no change (Shubrooks *et al.*, 1975) or an improvement (Coltart *et al.*, 1975). It, therefore, seems reasonable to suppose that prolongation of pre-ejection period by propranolol reflects a reduction in contraction velocity due simply to its activity as a beta-adrenoceptor blocking drug. The methods we have used are capable of distinguishing between slow contraction and incoordinate contraction, not only when they occur separately, but also when they occur together in the same patient. In contrast, both mechanisms cause pre-ejection period to be prolonged, and so cannot be distinguished using this latter method alone. It cannot be suggested, therefore, that left ventricular disease and drugs with a negat inotropic effect have the same action on myocardium merely because they both prolong th pre-ejection period.

Abnormalities of left ventricular function have also been related to the ratio PEP/LVET. This was shown, in a large group of patients with heart disease of different types, to correlate with ejection fraction (Garrard *et al.*, 1970). However, when patients with coronary artery disease alone were considered, there was no such correlation. This lack of correlation has since been confirmed by other workers (Parker and Just, 1974), though we were unable to confirm or deny this relation in the present study. Nevertheless, the demonstration of greatly increased cavity size, reduced amplitude of wall movement, and normal PEPI and PEP/LVET in patients with this diagnosis, makes it unlikely to have applied in our patients. Stack *et al.* (1976) has also described an even closer correlation between fractional shortening and PEP/LVET in patients with primary myocardial disease or coronary artery disease, which was not confirmed in the present study, the weak correlation demonstrated being of no clinical value in individual patients. It does seem, however, that the addition of ejection time in the ratio PEP/LVET increases the correlation with more widely measured variables such as Vcf or fractional shortening, compared with PEPI, at the expense of reducing its specificity as an index of incoordinate contraction.

The present results allow interpretations of previous observations on systolic time intervals to be extended. Pre-ejection period is prolonged in a proportion of patients with chronic ischaemic heart disease, particularly in those who develop left ventricular aneurysm (Jezek, 1963) or 'heart failure' (Weissler *et al.*, 1969a). Prolongation, to a lesser extent, may also occur in patients with angina pectoris even in the absence of other manifestations of left ventricular disease (Pouget *et al.*, 1971). These observations are all compatible with the incidence and associations of abnormal early systolic wall movement shown by angiography (Gibson *et al.*, 1978). After aortic valve replacement, increased PEP is explicable by an early period of incoordinate contraction caused by the operation itself (Seabra-Gomes *et al.*, 1976), comparable to that shown by echocardiography after aortic valve replacement by Venco *et al.* (1976). Alternatively, a reduction in PEP may occur, probably because of increased sympathetic activity, as shown by Matlof *et al.* (1973) after aortocoronary saphenous vein bypass grafting. Failure of PEP to shorten subsequently has been associated with the presence of either left ventricular disease or graft occlusion (Johnson *et al.*, 1972). Observations on changes in PEP after acute myocardial infarction are also in line with the present results, and are explicable on the basis of the separate effects of ventricular disease and adrenergic stimulation. By contrast, the echocardiographic methods that we have used may have value in studying such patients by virtue of their ability to separate these two effects and to detect incoordinate contraction even in the presence of increased sympathetic activity.

Study of left ventricular function by means of systolic time intervals has always been associated with persistent ambiguity. On the one hand, there is evidence to suggest that their measurement detects a clinically significant aspect of left ventricular function, while on the other hand they do not correlate closely with any of the routine haemodynamic or angiographic measurements usually made in patients with left ventricular disease. This discrepancy has led to doubt as to their value in the clinical assessment of patients with coronary artery disease (Parker and Just, 1974), since they fail to correlate with ejection fraction, 'contractility indices', or asynergy determined from inspection of ventriculograms. Demonstration of specific correlation with abnormal early systolic wall movement clarifies the genesis of prolongation of the pre-ejection period and thus will help with the interpretation of abnormalities of the systolic time intervals observed in patients with left ventricular disease. It may also be possible to use the large amount of published information based on measurement of the systolic time intervals to extend appreciation of the physiological significance of the normal synchronous left ventricular wall movement and to assess the clinical and epidemiological consequences of incoordinate contraction.

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Haemodynamic effects of acute beta-adrenergic receptor blockade in congestive cardiomyopathy

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SUMMARY Acebutolol ('Sectral'), a cardioselective beta-blocking drug, was administered intravenously in a dose of 25 mg to 10 patients with congestive cardiomyopathy. All of them were in a stable condition on antifailure regimens. The drug resulted in a statistically significant decline in left ventricular contractility as judged by peak left ventricular dP/dT and the contractility index. The mean aortic blood pressure also fell. There was a significant increase in end-diastolic and end-systolic left ventricular volumes.

Mean values for heart rate, ejection fraction, left ventricular stroke work index, and cardiac output also fell, but the results were not statistically significant. Left ventricular distensibility as judged by the slope of the diastolic pressure-volume relation also improved significantly.

A reduction in myocardial energy requirements, improved compliance, and lowering of arterial pressure would be haemodynamically advantageous. However, further cardiac dilatation and reduction in contractility—the basic defects in congestive cardiomyopathy—could lead to further deterioration.

Congestive cardiomyopathy is generally regarded as a syndrome caused by diverse aetiological agents (Connolly *et al.*, 1976). In the majority of cases the cause is unknown and current treatment grossly inadequate. Goodwin (1974) has stated that, 'at the present time the prognosis for severe congestive cardiomyopathy is so bleak and the treatment so unsatisfactory that cardiac transplantation may be considered in desperate cases'.

Waagstein *et al.* (1975) reported clinical improvement in 7 patients with congestive cardiomyopathy who were given oral beta-blocking drugs. These drugs were judged to have resulted in improvement on the basis of clinical signs, ergometrically-measured exercise capacity, and non-invasive tests of cardiac function. No haemodynamic data were presented. Since a priori, beta-receptor blockade should result in worsening of cardiac function in such patients, this was a paradoxical finding. It has major implications in the therapeutic management and pathophysiology of congestive cardiomyopathies as well as the action of beta-blocking agents.

This communication reports a haemodynamic study of 10 patients with congestive cardiomyopathy in whom beta-blockade was produced by the intravenous administration of a cardioselective beta-blocker, acebutolol ('Sectral').

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Subjects and methods

Ten patients were studied, 8 men and 2 women. The clinical and electrocardiographic findings together with medication at the time of study are listed in Table 1. The diagnosis of congestive cardiomyopathy was based on the criteria outlined by Goodwin and Oakley (1972).

Coronary artery disease, pericardial, valvular, and congenital heart disease were excluded by right and left heart catheterisation, angiocardiography, and selective coronary angiography. No patient was or had been hypertensive. Secondary cardiomyopathies were excluded by appropriate tests and infiltrative cardiac muscle lesions by haemodynamic studies and endomyocardial biopsy.

All patients had had at least one episode of frank congestive cardiac failure resulting from cardiac muscle dysfunction. The first 5 patients had not been in clinical cardiac failure for at least 1 month before study. The remaining 5 patients had suffered cardiac decompensation within this period. All were on antifailure regimens at the time of study, and none was in clinical failure.

(A) INVESTIGATION PROCEDURE

All patients were studied after an overnight fast and after informed consent had been obtained.

Table 1 *Clinical data*

Case no.	*Sex*	*Age (y)*	*Possible aetiology*	*Rhythm*	*QRS complex*	*Medication*
1	M	52	Alcohol	Sinus	Normal	Frusemide, digoxin, potassium
2	M	41	Alcohol	Sinus	Normal	Frusemide, digoxin, potassium
3	M	39	Idiopathic	Junctional	Left ventricular hypertrophy	Digoxin, frusemide, Slow K
4	M	49	Alcohol	Sinus	Left ventricular hypertrophy	Digoxin, frusemide, potassium
5	M	32	Alcohol	Sinus	Normal	Digoxin, frusemide, Slow K
6	M	38	Alcohol	Sinus	Normal	Digoxin, frusemide, Slow K
7	M	55	Idiopathic	Sinus with ventricular extrasystoles	Normal	Digoxin, frusemide, Slow K
8	M	29	Viral	Sinus	Normal	Digoxin, frusemide, Slow K
9	F	60	Alcohol	Sinus	Left ventricular hypertrophy	Digoxin, frusemide, Slow K
10	F	49	Idiopathic	Sinus	Left bundle-branch block	Digoxin, aldactone, frusemide

Premedication consisted of 10 mg intramuscular diazepam and 0·6 mg atropine.

Selective cine coronary angiography was performed according to the technique of Judkins (1967). Right heart catheterisation was then performed by the usual techniques.

Fifteen minutes after coronary angiography, duplicate determinations of cardiac output were made by the indicator dilution technique. Indocyanine green, 10 mg, was injected into the pulmonary artery while arterial blood was withdrawn at a constant rate through a Waters XC-301 cuvette densitometer via an aortic catheter. The densitometer was calibrated by the dynamic method (Sparling *et al.*, 1960).

Quantitative left ventriculography was next performed in the 30° right anterior oblique projection by injecting 50 ml meglumine ('Renografin') at a rate of 10 to 15 ml/s through an 8 French 'Pigtail' catheter introduced retrogradely across the aortic valve. Acebutolol ('Sectral'), 25 mg, was then administered via the pulmonary artery catheter. Fifteen minutes later, pressure measurement, cardiac output, and left ventriculography were repeated.

After the haemodynamic study, left ventricular endomyocardial biopsy was performed by the long sheath technique (Brooksby *et al.*, 1974) with a King's bioptome. The specimens were examined by light and electron microscopy.

(B) MEASUREMENTS

Left ventricular pressure was recorded via well-flushed catheters connected to a Bell and Howell strain gauge. The sternal angle was the zero reference. Left ventricular pressure was recorded at high speed (200 mm/s) and high gain (1 cm = 5 mmHg) as well as at 1 cm deflection equals 10 mmHg. The left ventricular pressure was digitised on a digitising table (Numonics Corp.) connected to a Wang 2200 S desk-top computer in order to obtain the pressure-based indices of left ventricular function.

(1) *Left ventricular volumes*

Left ventricular end-systolic and end-diastolic volumes were measured from the 30° right anterior oblique left ventriculogram by a special-purpose calculator (Bones and Ikram, 1977).

(2) *Systolic ejection fraction*

This was calculated from the systolic and diastolic volumes by means of the formula:

$$\frac{\text{End-diastolic volume} - \text{end-systolic volume}}{\text{End-diastolic volume}} \times 100$$

(3) *Left ventricular peak dP/dT*

The peak rate of rise of left ventricular pressure was measured from the high-speed pressure tracing (200 mms) by means of a computer programme.

(4) *Left ventricular stroke work index* (LVSWI)

This was calculated from the formula:

$$\text{LVSWI (g m/m}^2\text{ BSA/beat)} = \text{Stroke index} \times (\text{mean LV systolic pressure} - \text{LV end-diastolic pressure}) \times 0{\cdot}0136$$

(5) *Contractility index*

This index of left ventricular function was calculated from the formula:

$$\text{Contractility index (g m/cm}^3\text{per beat)} = \frac{\text{Stroke work}}{\text{LV end-diastolic volume}}$$

(6) *Mean left ventricular systolic pressure*

This was obtained by digitising the area beneath the systolic portion of the left ventricular pressure tracing and converting the result to millimetres of mercury.

(7) *Mean aortic pressure*

This was obtained directly from the aortic pressure amplifier by electrical damping of the pressure pulse.

(8) *Left ventricular end-diastolic pressure*

This was taken as the point where the left ventricular pressure pulse began its rapid upstroke on the high gain left ventricular pressure recording.

(9) *Left ventricular compliance*

In this study it was assumed that the left ventricular ressure-volume curve was exponential (Noble *et al.*, 1969; Gaasch *et al.*, 1972) and conformed to: $P = be^{kV}$. This can also be written $k = (\ln P - \ln b)/V$. In the formula P is the left ventricular end-diastolic pressure, V is the end-diastolic volume (ml/m²), b is the extrapolated left ventricular pressure at zero V, is the slope of the log P–V relation, and e is the base of the natural logarithm. The constant b cannot be measured easily in humans so it was assumed to be the same as that derived from animal studies, that is 0·43 mmHg. K (stiffness constant) is the slope of the P–V function and is independent of pressure as well as of large changes in ventricular size. It is slightly affected by changes in ventricular geometry (Diamond *et al.*, 1971). Compliance at end-diastole was calculated from the formula

$$dV/VdP\ (\text{mmHg}^{-1}) = dV/dP \times 1/V.$$

Statistical analysis was performed by Student's paired t test.

Results

The results are detailed in Tables 2 and 3.

(1) HEART RATE

There was an overall fall of 8 per cent in heart rate after acebutolol. This was not statistically significant.

Table 2 *Haemodynamic data before and after acebutolol*

Case no.	*Heart rate/min*		*Mean aortic pressure (mmHg)*		*Mean left ventricular systolic pressure (mmHg)*		*End-diastolic pressure (mmHg)*		*Cardiac index*		*End-systolic volume (ml/m²)*		*End-diastolic volume (ml/m²)*		*Ejection fraction (%)*	
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*
1	98	88	72	64	89	74	15	14	3·05	2·08	61	103	126	141	51	27
2	73	75	70	66	78	70	8	11	2·39	1·6	56	68	116	124	52	45
3	101	110	93	90	93	102	6	8	4·04	4·79	33	41	64	60	49	33
	74	72	75	68	142	140	35	32	3·8	2·6	64	75	126	138	49	47
	80	85	97	100	128	115	26	12	3·04	3·06	66	78	138	132	52	41
6	96	92	79	73	97	92	23	23	2·37	1·99	157	152	217	227	28	33
7	112	70	85	76	109	70	23	24	2·14	1·65	147	163	211	207	30	21
8	81	83	74	67	81	68	18	16	1·74	1·90	95	106	128	154	26	31
9	78	77	88	79	97	85	35	24	1·32	1·23	107	130	168	203	36	36
10	90	62	91	81	119	94	20	8	2·34	2·11	154	151	216	246	29	39
Mean	88·3	81·4	82·4	76·4	103·3	91·1	20·9	17·2	2·623	2·30	93·9	106·4	150·8	163·3	40·2	35·3
SD	13·1	13·5	9·64	11·6	20·9	23·4	9·8	8·1	0·86	1·01	45·3	41·5	50·9	56·5	11·3	8·03
P		NS		0·001		0·05		NS		NS		0·005		0·01		NS
Normal values		—		—		—		9 ± 4		—		24 ± 10		70 ± 12		67 ± 8
Reference		—		—		—		—		*		†		†		†

*Barratt-Boyes and Wood (1958). †Kennedy *et al.* (1966).

Table 3 *Haemodynamic data before and after acebutolol*

Case no.	*Stroke volume index (ml/beat per m²)*		*Left ventricular max dP/dT (mmHg/s)*		*Stiffness constant (K)*		*Stroke work index (g m/beat per m²)*		*Contractility index (g m/beat per cm³)*		*Compliance (mmHg⁻¹)*	
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*
1	31·2	23·6	1346	900	0·028	0·025	31·5	19·2	0·25	0·14	0·0187	0·0187
2	33·7	22·3	867	1021	0·026	0·026	31·2	17·5	0·27	0·14	0·0365	0·0280
3	41·3	40·6	1494	1567	0·043	0·048	66·3	55·4	1·03	0·92	0·0632	0·0427
4	51·9	36·2	1057	1083	0·034	0·031	76·3	52·5	0·64	0·38	0·0089	0·0022
5	38·0	36·0	1671	1473	0·030	0·025	51·0	54·2	0·37	0·41	0·0093	0·025
6	25·7	22·7	1510	856	0·018	0·017	24·7	20·5	0·11	0·09	0·0109	0·0109
7	19·1	23·6	1546	710	0·018	0·019	22·5	12·0	0·11	0·06	0·0109	0·0098
8	21·5	22·9	1190	713	0·028	0·023	16·3	16·4	0·13	0·11	0·0172	0·0172
9	18·0	13·7	950	1112	0·026	0·020	13·7	13·2	0·08	0·06	0·0064	0·0103
10	26·0	33·7	1119	1078	0·017	0·012	34·7	37·0	0·16	0·15	0·0130	0·0427
Mean	30·6	27·5	1275	1151	0·027	0·025	36·8	29·8	0·315	0·264	0·019	0·021
SD	10·8	8·49	276·8	413·3	0·0080	0·0098	21·08	18·1	0·302	0·267	0·018	0·013
P		NS		0·02		0·05		NS		0·05		NS
Normal values		—		1600 ± 400		0·047 ± 0·02		69 ± 25		⩾0·5		0·05 ± 0·02
Reference		—		—		*		†		‡		*

*Gaasch *et al.* (1972). †Snell and Luchsinger (1965). ‡Miller *et al.* (1965).

(2) EJECTION FRACTION
The ejection fraction fell by 8 per cent, this change again being statistically insignificant.

(3) END-DIASTOLIC VOLUME
There was a significant increase in end-diastolic volume of 10 per cent ($P < 0{\cdot}01$).

(4) END-SYSTOLIC VOLUME
This was increased by 21 per cent which was highly significant ($P < 0{\cdot}005$).

(5) MAXIMUM RATE OF LEFT VENTRICULAR PRESSURE RISE
This also fell significantly. The magnitude of the fall being 19 per cent ($P < 0{\cdot}02$).

(6) MEAN LEFT VENTRICULAR SYSTOLIC PRESSURE
There was a fall of 10 per cent in this variable ($P < 0{\cdot}05$).

(7) LEFT VENTRICULAR STROKE WORK INDEX
This index of left ventricular performance fell by 13 per cent but the magnitude of the fall was not significant.

(8) CONTRACTILITY INDEX
This index normalises the stroke work for change in ventricular volume. This fell significantly by 21 per cent ($P < 0{\cdot}05$) indicating significantly less work was performed per unit left ventricular volume.

(9) END-DIASTOLIC PRESSURE
This showed a small fall which was not statistically significant.

(10) CARDIAC INDEX
There was a 10 per cent fall in cardiac index. This was not significant.

(11) STROKE VOLUME INDEX
This also fell insignificantly (10%).

(12) MEAN CENTRAL AORTIC PRESSURE
There was a highly significant fall in mean aortic pressure of 7 per cent ($P < 0{\cdot}001$).

(13) STIFFNESS CONSTANT
This decreased by 10 per cent indicating decrease in stiffness. The result was significant at the 5 per cent level.

(14) LEFT VENTRICULAR COMPLIANCE
This measure of left ventricular compliance also altered in the direction of increased compliance (11%) but the result did not achieve significant levels.

Discussion

Acebutolol is a cardioselective beta-blocking drug with one-quarter to one-seventh the beta-blocking potency of propranolol (Lewis *et al.*, 1973). It also possesses intrinsic sympathomimetic activity. Hence it has similar pharmacological properties to alprenolol and practolol which were used by Waagstein *et al.* (1975) in their oral treatment of patients with congestive cardiomyopathy.

The dose of 25 mg was chosen because the haemodynamic response to 30 mg intravenously has been reported in normal subjects (Lewis *et al.*, 1973). Left ventricular contractility as judged by peak dP/dT and V max fell by 16 per cent and 14 per cent, respectively. There was little change in mean arterial pressure (2% fall) or left ventricular end-diastolic pressure (5% rise).

Waagstein *et al.* (1975) attributed much of the observed therapeutic benefit in their patients to a reduction of heart rate. They postulated that since left ventricular external work is equivalent to the product of heart rate and systolic blood pressure, a reduction in the former would reduce work load and also permit better diastolic filling.

The mean pretreatment heart rate was higher and the magnitude of the fall after treatment (19%) was greater than in our series (8%). This may be because their patients were deteriorating whereas ours were clinically stable. Premedication with atropine in our cases may also have contributed to the smaller fall in rate. None the less, beta-blockade results in some reduction in cardiac rate which may be beneficial.

The majority of our patients showed an increase in end-diastolic and end-systolic left ventricular volumes after beta-blockade, with a small reduction in systolic ejection fraction. These changes indicate a negative inotropic effect. They are in contrast to the observations of Waagstein *et al.* (1975) who noted a progressive reduction in radiographic cardiac size after beta-blockade. There are several inherent problems in the measurement of cardiac volumes by angiography, and they are accentuated in these patients with their very large and poorly contracting left ventricular silhouettes. However, non-angiographic radiological methods have also shown an increase in the heart size of normal subjects after beta-blockade (Chamberlain, 1966).

Stroke volume increased in 3 patients and fell in 7, the overall change being a fall of 3 per cent. This was not statistically significant nor was the

10 per cent fall in cardiac index. Waagstein *et al.* (1975) speculated that a reduction in tachycardia would allow better diastolic filling and thus increase stroke volume. Our results indicate that this does happen in some patients, but the increase is small and unpredictable.

Myocardial contractility as judged by peak rate of rise of left ventricular pressure fell significantly in all but 2 cases. This is in keeping with the well-known effects of beta-blocking drugs. Left ventricular stroke work showed some fall with beta-blockade, but the results were not statistically significant. Stroke work per unit of end-diastolic volume ('contractility index'), another measure of myocardial contractility, showed a significant fall. These findings indicate a decline in contractility. Since cardiomyopathic patients already suffer from impaired contractility, it is arguable that beta-blockade would be harmful. On the other hand, since contractility is a major determinant of myocardial energy requirements, a decrease would reduce the heart's energy needs.

The systemic arterial blood pressure fell in all patients, the fall being highly significant statistically. Waagstein *et al.* (1975) also reported a fall in blood pressure 3 to 7 days after oral beta-blockade. Since systolic arterial pressure is a determinant of myocardial energy needs, a fall would diminish the work load of the left ventricle.

Left ventricular compliance has been shown to be reduced in patients with congestive cardiomyopathy (Gaasch *et al.*, 1972). The effect of beta-blockade on compliance in these patients has not been previously reported. Though there are several practical and theoretical problems in the measurement of compliance, this study suggests that beta-blockade may improve compliance. This tends to improve filling and reduce end-diastolic pressure.

Waagstein *et al.* (1975) quote the prolonged bed-rest regimen of McDonald *et al.* (1972) in support of their hypothesis that reduction of myocardial work is of therapeutic benefit. These authors put patients with congestive cardiomyopathy to bed for periods ranging from an average of 73 to 239 days. They observed relief of symptoms and a reduction in heart size which was proportional to the duration and degree of bed rest. Our study confirms that beta-blockade decreases most of the determinants of cardiac work, that is rate, systolic blood pressure, and contractility. However, in our experience, these theoretically beneficial changes are accompanied by further cardiac dilatation and decline in contractility —an apparent worsening of the basic defects in congestive cardiomyopathy.

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Relation of plasma aldosterone concentration to diuretic treatment in patients with severe heart disease

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SUMMARY To assess the relation of hyperaldosteronism and potassium depletion to the intensity of diuretic therapy we have measured plasma aldosterone by radioimmunoassay and total exchangeable potassium by radioisotope dilution in 24 patients when they were stable at the end of their preparation for cardiac operation.

Some patients required intensive frusemide therapy to reach an optimal state for operation and many showed hyperaldosteronism. Plasma aldosterone was significantly related to daily dose of frusemide ($r=0{\cdot}77$).

Depletion of total exchangeable potassium expressed in terms of predicted weight was significantly related to plasma aldosterone ($r=-0{\cdot}64$). The reduction in total exchangeable potassium is interpreted as chiefly related to loss of lean tissue mass from the wasting that leads to cardiac cachexia, but evidence is presented on the basis of measurements of extracellular fluid volume as sulphate space (20 patients) of entry of sodium into the cells which may indicate a true cellular potassium loss.

Although plasma potassium is usually easily maintained with oral potassium supplements or aldosterone antagonists, we postulate that intensive diuretic therapy in severe heart disease may provoke hyperaldosteronism which accentuates potassium loss and may contribute to wasting and to intracellular potassium depletion in critical tissue, such as myocardium.

The fluid retention which is characteristic of chronic congestive heart failure arises from a disturbance of the homeostatic control of body sodium content (Merrill, 1946), mediated in part by the renin-angiotensin-aldosterone system which produces sodium retention in the distal renal tubule at the expense of loss of potassium and hydrogen ions. Until recently the part played by aldosterone has been difficult to define, partly because of technical factors as pointed out by Nicholls *et al.* (1974) and partly because of the paradoxical effect of diuretic therapy, which in the early stages of treatment of congestive failure reduces the activity of the renin-angiotensin-aldosterone system (Laragh, 1962; Genest *et al.*, 1968; Nicholls *et al.*, 1974), in contrast to the stimulation found with diuretics in normal subjects and in patients with hypertension (Laragh *et al.*, 1972). There is also a suggestion that the activity of the renin-angiotensin-aldosterone system is increased in heart failure as part of the general increase in sympathetic activity under these circumstances (Brod, 1972; Davis, 1974). Aldosterone antagonists are often recommended in treatment to prevent both sodium retention and potassium loss; they may be particularly useful for chronic treatment in the dried-out state, as Nicholls *et al.* (1974) have shown that hyperaldosteronism is a major feature in patients approaching dry weight on continued diuretic treatment.

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Potassium depletion shown by a reduction in total exchangeable potassium is a major feature of patients with severe heart disease on diuretic treatment (White *et al.*, 1969) and has been thought to contribute to the risks of surgical correction (Lockey *et al.*, 1966). However, more recent studies of total body potassium (Davidson *et al.*, 1976; Lawson *et al.*, 1976) measuring the natural radioisotope (^{40}K) in a total body counter suggest that tissue potassium is only slightly depleted in relation to body size. The reduction in total exchangeable potassium may be, in the main, an indication of a loss of lean body mass as part of wasting which may be occult (Walesby *et al.*, 1978) or evident in the extreme as 'cardiac cachexia', but local critical reductions in intracellular K concentration cannot be excluded (Hamer, 1977). The plasma potassium seems to be part of a labile component of the body potassium which varies without relation to total body stores (Croxson *et al.*, 1972; Nagant de Deuxchaisnes and Mach, 1974; Nicholls *et al.*, 1976) and cannot be used to predict potassium depletion. Plasma potassium may be relatively easily maintained by dietary supplements or aldosterone antagonists with relatively little effect on tissue potassium (White, 1970; Croxson *et al.*, 1972; Davidson and Gillebrand, 1973; Kremer *et al.*, 1977). It is important to maintain a normal plasma potassium in patients being treated with digitalis as the tendency of digitalis to produce arrhythmias is potentiated by hypokalaemia (Naylor, 1975; Steiness and Olesen, 1976).

Aldosterone antagonists may be more effective than dietary supplements of potassium in the long-term correction of tissue potassium losses (Croxson *et al.*, 1972; Davidson and Gillebrand, 1973; Kremer *et al.*, 1977), perhaps on the basis of correcting cellular magnesium depletion (Lim and Jacob, 1972, 1978; Dyckner and Wester, 1978). With the possibility of the need for treatment with aldosterone antagonists in mind, the availability of a practicable and sensitive radioimmunoassay for plasma aldosterone led us to investigate the aldosterone and electrolyte status of our patients awaiting cardiac surgery.

Methods

We studied 24 patients (10 men and 14 women) mostly with valve disease (Table 1) being prepared in hospital for surgical treatment. The patients agreed to take part in the study after a full explanation of the detailed procedure and assurance that their operation would not be delayed or otherwise affected by the study. All were in a stable state after optimal treatment (Table 2) to reduce oedema and pulmonary congestion, as judged by constant body weight, and were studied in the few weeks between admission to hospital and operation; 2 patients (cases 22 and 24) had slight detectable residual oedema. Ethical considerations forbade any change in diuretic treatment or in general ward management; all patients received normal ward diet with 'no added salt' at the table and unlimited fluid intake. In all but 4 patients (cases 4, 7, 9, and 12) diuretic therapy was thought necessary and was sometimes intensive (Table 2).

Table 1 *Details of patients studied*

Case no.	*Age and sex*	*Height (cm)*	*Weight (kg)*	*Predicted weight (kg)*	*Weight of % predicted*	*Diagnosis*
1	47 F	173	67·1	70·3	95	Mitral valve disease (mixed lesions)
2	62 M	169	65·4	71·0	92	Aortic stenosis
3	59 F	153	59·0	59·3	100	Aortic valve disease (mixed lesions)
4	49 M	170	77·1	73·0	106	Mitral regurgitation
5	67 M	160	75·3	64·4	117	Aortic stenosis, ischaemic heart disease
6	64 F	170	63·0	71·2	89	Mitral and aortic valve disease (mixed lesions)
7	51 M	168	52·2	71·2	73	Aortic valve disease (mixed lesions)
8	68 F	163	46·7	65·8	71	Mitral and tricuspid valve disease (mixed lesions)
9	34 F	163	42·0	59·9	70	Mitral valve disease (mixed lesions)
10	45 M	164	64·1	68·0	74	Mitral and aortic valve disease (mixed lesions)
11	30 M	178	57·5	77·1	75	Mitral stenosis
12	64 M	173	85·7	73·9	116	Aortic valve disease (mixed lesions)
13	62 M	165	72·2	68·0	106	Aortic stenosis
14	60 F	155	45·4	60·8	75	Mitral and aortic valve disease (mixed lesions)
15	50 M	164	59·2	68·5	86	Ischaemic heart disease, mitral regurgitation, ventricular septal defect
16	64 F	164	52·5	66·7	79	Mitral valve disease, tricuspid regurgitation, aortic valve disease
17	46 F	155	53·4	59·0	91	Mitral valve disease
18	62 F	160	51·0	64·0	80	Mitral valve disease
19	45 F	156	45·8	59·6	77	Mitral and aortic valve disease
20	60 F	167	60·2	69·4	87	Mitral valve disease, aortic regurgitation
21	61 F	155	79·5	60·8	131	Ischaemic heart disease, aortic valve disease
22	56 F	160	61·0	63·5	96	Ischaemic heart disease, coarctation
23	55 F	151	34·5	58·3	59	Mitral valve disease
24	69 M	163	55·5	66·2	84	Ischaemic heart disease

We attempted to maintain normal plasma potassium concentrations with potassium supplements (Slow K) or amiloride where necessary.

Total exchangeable potassium and sodium were estimated simultaneously with ^{43}K and ^{24}Na as suggested by Davies and Robertson (1973), but injecting 100 μCi ^{43}K and 20 μCi ^{21}Na to produce acceptable counting times.

^{43}K was obtained from the Medical Research Council Cyclotron Unit, Hammersmith Hospital, and the ^{24}Na from the Radiochemical Centre, Amersham. Activities were checked using a standard ionisation chamber. With the patient recumbent 30 ml blood were drawn into lithium heparin tubes without forearm exercise and venous occlusion as

Table 2 *Diuretic therapy*

Case no.	*Frusemide (mg/day)*	*Amiloride (mg/day)*	*Slow-K (mg/day)*	*Navidrex-K (tablets/day)*	*Aldosterone (pmol/l)*
1				2	180
2				2	222
3				2	266
4					278
5	40		1200		305
6	40	5			333
7					389
8				1	416
9					416
10	40	5			472
11	160	20			638
12					694
13	80	10			833
14	40		3600		1457
15	80	10			1665
16	160	15			1721
17	40	10			1804
18	40	5			1887
19	40				2359
20	80	10			2914
21	240	30			3053
22	1000	20			3608
23	320	20			4856
24	1000	15			6244

recommended by Brown *et al.* (1970); 20 ml were spun down and stored at –20°C for plasma aldosterone estimation; the remainder was used for the plasma electrolyte estimations. Twenty µCi ^{24}Na and 100 µCi ^{43}K (prepared by weight using strict aseptic procedures) were injected together in the same syringes. In 20 patients 30 µCi ^{35}S as sulphate were added for sulphate space estimation. After the intravenous injections all swabs, syringes, washes, etc., were counted against standards to account for the non-injected activity, the standards (^{24}Na, ^{43}K) being prepared by weight. Blood samples were taken without venous occlusion or forearm exercise at 1, 2, 3, and 4 hours for sulphate space determination, and again at 24 and 26 hours for potassium estimation with the mean of the 2 results being reported as the total exchangeable potassium. In 5 patients (see Table 4) the 2 values for total exchangeable potassium differed by more than 15 per cent of the mean, and these patients were excluded from the regression analysis. The excretion of ^{43}K and ^{24}Na in the first 24 hours was assumed to be 3 per cent (Oleson, 1967; White *et al.*, 1969). The calculation of total exchangeable sodium and total exchangeable potassium was carried out using a Hewlett Packard 9810A proprogrammable calculator, with correction for radioactive decay during the counting period. Plasma sodium and potassium concentrations were taken as the mean of 2 values obtained by flame photometry. A predicted value for total exchangeable potassium (TEK) was obtained for each patient from a regression equation of log$_e$ (TEK) on log$_e$ height derived from normal subjects by Flear *et al.* (1966).

Total body water was estimated as 'cation space', the volume occupied by the sum of total exchangeable sodium (TENa) (representing mainly extracellular fluid) and total exchangeable potassium (TEK) (representing mainly cell water), dividing total cation (TENa + TEK) by extracellular (i.e. plasma) total cation concentration (Na + K) expressed in terms of extracellular water and assuming osmotic equilibrium between cells and extracellular fluid (Oleson, 1967). We measured extracellular fluid volume as sulphate space, using the method of Savoie and Jungers (1965) as outlined by White *et al.* (1969), modified by using a new xylene-based liquid scintillator (NE 260, Nuclear Enterprises) to which plasma can be added directly without protein precipitation. Plasma was stored for 7 days in a deep freeze to ensure complete decay of ^{24}Na and ^{43}K before counting and ^{35}S was counted in a Beckman automatic liquid scintillation counter. The observed sulphate space was corrected for plasma water content, Donnan equilibrium, and the entry of radiosulphate into red cells by multiplying by a factor of 0·93, differing from the value of 0·87 used by White *et al.* (1969) as plasma proteins are not now removed before measurement.

Extracellular sodium was calculated by multiplying the corrected sulphate space by the overall extracellular fluid sodium concentration, estimated as plasma sodium multiplied by 1·02 (White *et al.*, 1969). The residual sodium, that is sodium in cells or to a small extent elsewhere not exchanging with the extracellular fluid (Leaf, 1974), was calculated as the difference between total exchangeable sodium and extracellular sodium.

Plasma aldosterone was determined by the radioimmunoassay procedure described by Jowett *et al.* (1973). 1,2^{3}H-aldosterone (50 Ci/mmol) was obtained from the Radiochemical Centre, Amersham, and from New England Nuclear. D-aldosterone was obtained from Koch-Light Laboratories and chromatography carried out using the Bush B5 system on Whatman's SG81 silica gel-impregnated paper. Antibody to aldosterone-3-carboxymethoxime conjugated to bovine serum albumin was donated by Dr J. D. H. Slater (Middlesex Hospital) and used at a final dilution of 1 :600. Standard curves were set from 0 to 160 pg/ml aldosterone.

Aldosterone assays were carried out in duplicate and the duplicate variation was between 1 and 2 per cent. Each sample was assayed on three separate occasions and the interassay variation was 10 per cent. A water blank was included with each batch of samples being assayed; blank values were always less than 6 pg/ml.

Aldosterone levels were measured in 8 normal

Table 3 *Cardiac catheterisation findings*

Case no.	*Mean wedge pressure (mmHg)*	*Right atrial pressure (mmHg)*	*Pulmonary artery pressure mean (mmHg)*	*Pulmonary vascular resistance (units)*	*Cardiac output (l/min)*	*Aldosterone (pmol/l)*
1	35	8	65	10·0	3·0	180
2	7	2	23	2·0	8·0*	222
4	22	5	28	1·9	3·2	278
6	24	6	31	2·4	2·9	333
8	20	6	35	4·3	3·5	416
10	8	5	13	1·2	4·2	472
11	29	3	38	2·3	4·0	638
12	10	5	18	1·6	5·0	694
14	18	7	55	10·0	3·7	1457
15	23	18	45	11·0	2·9	1665
16	25	8	45	5·0	4·0	1721
17	15	6	33	7·4	2·3	1804
18	24	6	32	3·2	2·5	1887
19	25	6	38	4·2	3·1	2359
20	28	7	75	11·8	4·0	2914

* High output attributed to extensive Paget's disease.

volunteers between 12 noon and 2 pm, the blood being taken with the subject recumbent after at least 4 hours in the erect posture.

In 15 patients cardiac catheterisation was carried out as part of their preoperative assessment (Table 3).

Results

The detailed findings, including plasma electrolyte values, are listed in Table 4 in order of plasma aldosterone concentration.

BODY WEIGHT

Eighteen of the patients (75%) were below the average weight for their age, sex, and height (Society of Actuaries, 1959).

POTASSIUM

The plasma potassium was in the normal range for all but 2 of our patients with a range of 3·55 to 5·50 mmol/l and a mean of 4·20 mmol/l for the group.

Exchangeable potassium was reduced compared with the predicted value in terms of expected weight in 12 patients and was below 70 per cent of the predicted value in 5. There was a significant correlation between total exchangeable potassium depletion, expressed as a percentage of predicted, and weight, expressed as a percentage of predicted on the basis of height ($r = 0·56$, $P < 0·02$).

SODIUM

Three patients had plasma sodium levels below 130 mmol/l. The range for the whole group was 121·5 to 145·5 mmol/l with a mean of 137·5 mmol/l.

The predicted total exchangeable sodium was calculated for men from the regression $\log_e$ total exchangeable sodium on $\log_e$ height and also on $\log_e$ weight derived from normal subjects by Flear *et al.* (1966). No calculation was made for women as the correlation coefficients for the regression $\log_e$ total exchangeable sodium on $\log_e$ height and on $\log_e$ weight found by Flear *et al.* (1966) were very low.

Total exchangeable sodium was raised in 8 of the men with a mean of 14·1 per cent above predicted from height and was 9·4 per cent above predicted from weight for the whole group of 10 men.

CATION SPACE

This quantity, which is calculated from the sum of total exchangeable sodium and total exchangeable potassium, may be regarded as an estimate of total body water. Cation space expressed as a percentage of body weight averaged 67·4 per cent for the men and 58·6 per cent for the women. These findings are considerably greater than the values for total body water expressed as a percentage of body weight derived from normal subjects by McMurray *et al.* (1958) of 54·3 per cent for men and 48·6 per cent for women.

SULPHATE SPACE

Sulphate space, an estimate of extracellular fluid volume (Table 4), expressed as a percentage of body weight, gave a mean for the men of 19·4 per cent and for the women of 21·1 per cent. Standard values for normal subjects are 21·3 per cent and 17·4 per cent, respectively (Savoie and Jungers, 1965); so, on average, our patients showed little deviation from the normal.

Sulphate space expressed as a percentage of predicted was not related to total exchangeable sodium expressed as a percentage of predicted and there was no correlation between sulphate space (i.e. extracellular fluid volume) and any of the cardiac catheterisation measurements.

ALDOSTERONE

The results in 8 normal controls were 278, 302, 291, 272, 413, 563, 161, and 250 pmol/l (100, 109, 105, 98, 149, 203, 58, and 90 ng/l) (mean 316 pmol/l (114 ng/l) and standard deviation ±114 pmol/l (±41 ng/l)); these findings agree well with those published for erect subjects on normal diets: 366±247 pmol/l (132±89 ng/l) (Mayes *et al.*, 1970); 522±69 pmol/l (188±25 ng/l) (Bayard *et al.*, 1970); 413±175 pmol/l (149±63 ng/l) (Farmer *et al.*, 1973); 372±283 pmol/l (134±102 ng/l) (McKenzie and Clements, 1974); and 311±302 pmol/l (112±109 ng/l) (Castro *et al.*, 1974).

Table 4 *Aldosterone and electrolyte results*

Case no.	*Plasma sodium (mmol/l)*	*Plasma potassium (mmol/l)*	*Total exchangeable sodium (mmol/l)*	*Total exchangeable potassium (mmol/l)*	*Total exchangeable potassium predicted (mmol/l)*	*Total exchanageable potassium as % of predicted*	*Sulphate space (l)*	*Aldosterone (pmol/l)*
1	140·0	3·70	3333	3122	2690	116	17·7	180
2	141·0	4·00	3517	3538	3040	116	16·6	222
3	138·5	3·55	2201	2052	2180	94	9·3	266
4	140·0	3·90	3453	5655*	3050	185	18·3	278
5	139·5	3·80	3285	3293	2660	124	14·2	305
6	143·0	4·45	2682	2813	1970	143	13·3	333
7	140·0	4·35	2683	3050	2840	107	11·3	389
8	128·5	4·35	1929	1859*	1840	101	11·7	416
9	138·5	4·90	2394	2372	2420	98	14·4	416
10	145·5	3·90	1368	3798*	2820	135	12·3	472
11	141·5	3·65	4495	2684	3430	78	10·8	638
12	140·0	4·35	3402	3507	3190	110	18·3	694
13	140·0	4·40	3017	2928	2860	102	13·7	833
14	139·5	4·75	1714	1443	2220	65	—	1457
15	138·5	4·75	2616	2567	2820	91	11·7	1665
16	133·5	3·95	2309	1755	1860	94	11·3	1721
17	138·0	3·90	2270	2181	2220	98	11·2	1804
18	136·5	4·05	2012	1453	1790	81	10·0	1887
19	142·0	4·30	1803	1564	2250	66	—	2359
20	139·0	3·70	2507	1148	1920	60	14·9	2914
21	136·5	4·30	4071	2142	1700	126	13·5	3053
22	136·5	3·90	3819	2634	2350	115	13·7	3608
23	124·0	5·50	1624	1358*	2120	64	—	4856
24	121·5	4·80	3073	1636*	2980	55	—	6244

* In these patients duplicate estimates of total exchangeable potassium differed by more than 15 per cent of the mean and they are excluded from the regression analyses.

The levels in our patients (Tables 2, 3, 4, and 5) fall into 3 groups: 13 patients with normal or slightly raised levels up to 833 pmol/l (300 ng/l), a middle range (6 patients) with values between 833 and 2775 pmol/l (300 and 1000 ng/l), and a high range above 2775 pmol/l (1000 ng/l) (5 patients). In view of the wide variation in plasma aldosterone concentrations, regression analyses were carried out to determine whether any of our other measurements showed a relation to the plasma aldosterone expressed logarithmically.

There was a poor correlation between $\log_{10}$ aldosterone concentration and plasma potassium ($r = 0{\cdot}40$), but $\log_{10}$ aldosterone concentration correlated negatively with plasma sodium ($r = -0{\cdot}5$, $P < 0{\cdot}01$).

Various methods for the correction of total exchangeable potassium (TEK) for body size made little difference and a similar relation was found between $\log_{10}$ aldosterone concentration and unmodified total exchangeable potassium ($r = -0{\cdot}63$, $P < 0{\cdot}01$), total exchangeable potassium/metre height ($r = -0{\cdot}64$, $P < 0{\cdot}01$) (Fig. 1), and total exchangeable potassium/kg body weight ($r = -0{\cdot}59$, $P < 0{\cdot}01$). There was no correlation between total exchangeable sodium and plasma aldosterone concentration.

There was a negative relation between $\log_{10}$ plasma aldosterone concentration and sulphate space ($r = -0{\cdot}29$) (Fig. 2) which did not reach significant levels even for the subgroup of 9 men with sulphate space expressed as a percentage of body weight ($r = -0{\cdot}46$, $P < 0{\cdot}1$).

Residual sodium was not related to $\log_{10}$ aldosterone concentration or total exchangeable potassium expressed per metre height, and similar results were obtained expressing residual sodium in terms of body weight.

There was no correlation of $\log_{10}$ aldosterone concentration with cardiac output and the correlations with mean pulmonary artery pressure ($r=0{\cdot}33$), pulmonary wedge pressure ($r=0{\cdot}33$), and right atrial pressure ($r=0{\cdot}36$) were not significant.

DIURETIC THERAPY

A highly significant correlation was found in patients on frusemide between $\log_{10}$ frusemide and aldosterone concentration ($r=0{\cdot}77$, $P<0{\cdot}001$) (Fig. 3). The use of log frusemide dose necessarily excludes patients not on frusemide from this correlation. The correlation with $\log_{10}$ amiloride dose did not achieve significance ($r=0{\cdot}51$, $P<0{\cdot}1$).

Discussion

ROLE OF ALDOSTERONE IN CONGESTIVE HEART FAILURE

The part played by aldosterone in the different stages of congestive heart failure in relation to the response to diuretic therapy has been clarified with the measurement of plasma aldosterone by Nicholls *et al.* (1974), and the findings can be interpreted in relation to the two major stimuli to renin release; a reduction in the effective arterial volume and a fall in the sodium load reaching the distal tubule (Vander, 1967). At the *onset of heart failure* and in the untreated situation a moderate increase in plasma aldosterone is expected as part of the increase in sympathetic activity (Brod, 1972) and the primary stimulus to fluid retention (Davis, 1974) from a fall in effective arterial volume or a reduced sodium load in the distal tubule after enhanced reabsorption proximally.

During diuresis plasma aldosterone is suppressed to very low levels. The attribution of this response to a reduction in the initial stimulus as cardiovascular performance improves seems unlikely in view of the lack of haemodynamic improvement noted after diuretic therapy by Stampfer *et al.* (1968). The dramatic increase in sodium load to the distal tubule during diuresis seems to outweigh the effect of a fall in effective arterial volume at this stage in the treatment of heart failure. As the patient approaches *dry weight* plasma aldosterone rises again. It may be that continued diuretic treatment after loss of oedema further reduces effective circulating arterial volume, and the sodium load reaching the distal tubule will be less than in the diuretic phase. It has been suggested that reduced catabolism of aldosterone from impaired hepatic function plays a part in producing the high plasma aldosterone concentration in congestive heart failure (Yates *et al.*, 1958; Tait *et al.*, 1965; Genest *et al.*, 1968), but Nicholls *et al.* (1974) found that plasma renin activity changed in parallel with the plasma aldosterone concentration, suggesting that the 'renin-angiotensin-aldosterone' system continues to operate.

RADIOISOTOPE METHODS

Oleson and Valentin (1973) confirmed the general validity of the radioisotope dilution method for total exchangeable potassium in the investigation of patients with treated heart failure. The apparent discrepancy with measurements of total body potassium from natural ^{40}K in a whole body counter is probably related to differences in interpretation (Hamer, 1977). The finding of near normal total body potassium in relation to current weight (Davidson *et al.*, 1976; Lawson *et al.*, 1976) is in keeping with the suggestion of Nagant de Deuxchaisnes *et al.* (1961) and Nagent de Deuxchaisnes and Mach (1974) that the loss of potassium seen with total exchangeable potassium measurements is a 'pseudodepletion' caused by loss of lean body mass. The main bulk of body potassium is contained in skeletal muscle. Because of the variable effects of fluid retention, obesity, and loss of lean tissue from cardiac cachexia the lean body mass bears no fixed relation to body weight in treated severe heart disease (Rich and Wright, 1978). Our assessments of depleted total exchangeable potassium are based on estimates of normal body size derived from height and are consistent with loss of lean body mass (White *et al.*, 1969).

The suggestion of Oleson and Valetin (1973) that sodium did not enter cells to replace lost potassium in treated heart failure may be the result of technical problems related to their use of ^{82}Br, an analogue of the chloride (Cl) ion as a marker of extracellular fluid volume (Hamer, 1977). The sulphate ion used here has advantages for the measurement of extracellular fluid volume in that it does not penetrate cells to a significant extent, but measurement is more complicated as back-extrapolation of the data to the time of injection is needed to allow for renal excretion of sulphate (Savoie and Jungers, 1965). The evidence that many patients have larger total exchangeable sodium than accounted for by sodium in the extracellular fluid (Fig. 4) indicates some entry of sodium into the cells consistent with a fall in intracellular potassium concentration, the 'true depletion' of Nagant de Deuxchaisnes *et al.* (1961) and Nagent de Deuxchaisnes and Mach (1974) as shown for skeletal muscle in primary hyperaldosteronism by Milne *et al.* (1967), and in Bartter's syndrome by Delaporte *et al.* (1978). The absence of such findings in our previous study (White *et al.*, 1969) on similar patients may relate to the difficulty of measurement of small changes when 'pseudodepletion' is the dominant factor. Though muscle wasting from the process of malnutrition (Walesby *et al.*, 1978) that leads to 'cardiac cachexia' seems to play a major role in reducing total exchangeable potassium from loss of lean body mass (i.e. a 'pseudodepletion'), some 'true depletion' producing a reduction of intracellular potassium concentration is difficult to exclude and could be of critical importance in the myocardium, changing the membrane potential to produce fatal ventricular arrhythmias as stressed by Lockey *et al.* (1966), though Oleson and Valentin (1973) failed to confirm any increased risk of death from arrhythmias with reduced total exchangeable potassium in their patients. Myocardial biopsies at operation show reduced cell potassium concentration (Schimert *et al.*, 1966), but Taggart and Slater (1970) have shown that similar changes may occur during operation, so they may not represent the preoperative state, and Ward and Cameron (1978) have shown in animals that the myocardium is relatively protected against potassium depletion.

The state of many of our patients on continued diuretic treatment after the loss of most of their oedema corresponds to the dried-out stage described by Nicholls *et al.* (1974) in which hyperaldosteronism is frequent.

Care was taken to ensure that the patients had reached a steady state, as far as the diuretic regimen was concerned, as indicated by a constant body weight and the patients were studied after several hours in the sitting position to minimise the effects of posture on plasma aldosterone. The very high concentrations found in some patients were in and beyond the range (up to 2 nmol/l = 720 ng/l) found by Nicholls *et al.* (1974) after relatively short periods of diuretic treatment in patients approaching dry weight, and are far beyond the range expected from postural variations. The 'no added salt' diet may have acted as a stimulus to renin secretion, producing a secondary rise in plasma aldosterone concentration. Though they were generally free from oedema our patients did not show extreme sodium depletion. There was also evidence from the tendency to a raised total exchangeable sodium in the men studied, from the increased cation space, and from the absence of any general fall in extracellular fluid volume (sulphate space), of persisting expansion of the extracellular fluid. Nevertheless, it is difficult to exclude a reduction in effective arterial volume provoking secretion of renin and a consequent hyperaldosteronism; such a change is suggested by the higher plasma aldosterone levels with reduced sulphate space and may be obscured in measurements of total extracellular fluid volume by a persisting increase in the volume of the venous compartment and the pulmonary circulation. The absence of any correlation between plasma aldosterone and cardiac output may indicate that blood flow is not the critical factor, but is more likely to reflect the different conditions of study.

Previous studies (White, 1970) have shown that potassium supplements have only a partial effect in correcting the reduced total exchangeable potassium in keeping with the description of hypokalaemia as a simple potassium 'deficiency' by Nagant de Deuxchaisnes *et al.* (1961) and Nagant de Deuxchaisnes and Mach (1974), suggesting that treatment directed to reversing hyperaldosteronism might be a more useful approach to correcting potassium losses in the present situation. Relatively short-term treatment with amiloride has only a minor effect on tissue potassium (Croxson *et al.*, 1972; Davidson and Gillebrand, 1973; Kremer *et al.*, 1977) and attempts to correct potassium depletion caused by loss of lean body mass may be inappropriate, short of haemodynamic correction. We are hopeful that more prolonged treatment or other approaches such as reducing cardiac load by chronic vasodilator therapy (Chatterjee *et al.*, 1976), or a metabolic approach by correcting magnesium depletion (Dyckner and Wester, 1978; Lim and Jacob, 1978), or the insulin and glucose regimen (Majid *et al.*, 1972) may restore potassium to the cells effectively; further study is clearly necessary to determine the best approach to management of these severely affected patients.

INTERPRETATION OF PRESENT FINDINGS

We were concerned to assess the aldosterone situation in our patients with treated heart disease in relation to their preparation for operation, and we did not think it ethically justifiable to modify the conditions of treatment or to defer the patients' operations for the study. We are forced to argue the sequence of events from the results in individual patients with widely differing degrees of impairment (Table 1). In view of the fundamental similarity of the disturbed physiology leading to congestive heart failure, and as no clear separation of high and low plasma aldosterone levels was evident in our results we used regression analysis to determine the relations between the status or treatment of our patients and the biochemical measurements.

Patients on spironolactone were excluded to avoid possible interference with the aldosterone assay by metabolites but we were able to maintain normal plasma potassium levels with oral potassium supplements or amiloride where necessary in our patients. It seems unlikely that potassium administration played a part in provoking aldosterone secretion in our patients. The effect described by

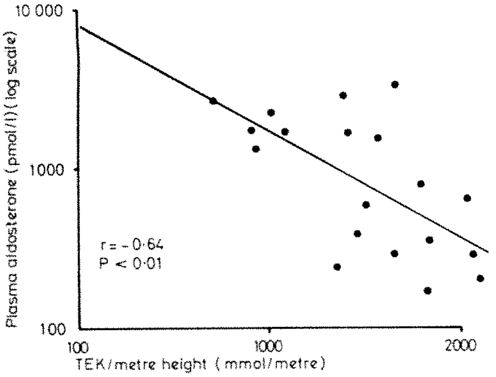

Fig. 1 *Relation of plasma aldosterone concentration to total exchangeable potassium (TEK). TEK is expressed in terms of height to correct for variations in body size in the presence of cachexia. High plasma aldosterone concentrations (log scale) are associated with potassium depletion as shown by the negative correlation ($r = -0{\cdot}64$, $P < 0{\cdot}01$).*

Laragh and Stoerk (1955) seems to be mediated by a direct action on the adrenal cortex, and the tendency to cellular potassium depletion in our patients might have the reverse effect, as suggested by Brunner *et al.* (1970).

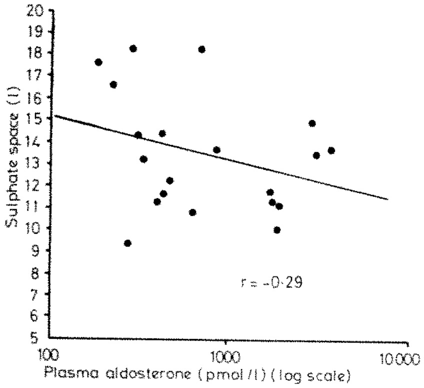

Fig. 2 *Relation between plasma aldosterone concentration (log scale) and extracellular fluid volume measured as sulphate space. The negative correlation ($r = -0{\cdot}29$) which does not achieve statistical significance suggests that hyperaldosteronism is associated with reduced extracellular fluid volume.*

A positive feedback effect of aldosterone antagonism leading to further aldosterone secretion as reported in Conn's syndrome (Kremer *et al.*, 1977) and in heart failure (Nicholls *et al.*, 1976) could frustrate attempts to correct potassium loss and may have played a contributory part in the hyperaldosteronism of some of our patients, though the correlation of plasma aldosterone with amiloride dose ($r = 0{\cdot}51$) did not reach significance in the relatively few patients receiving this treatment (Table 2).

IMPLICATIONS OF POTASSIUM DEPLETION IN DIURETIC THERAPY

Previous studies (Lockey *et al.*, 1966; Hocking and Bain, 1974) have been interpreted as indicating an association between intensive diuretic therapy and potassium depletion. However, Edmondson *et al.* (1974) concluded from a study of leucocyte electrolytes in cardiac and non-cardiac patients receiving diuretics that the heart disease rather than its treatment was responsible for the potassium depletion in cardiac patients, but their results are obscured by an apparent failure to consider the effects of digitalis glycosides which will also tend to deplete the leucocyte potassium concentration and may account for the difference between the 2 groups of patients (Astrup, 1974). We show here a clear relation between intensive diuretic therapy, hyperaldosteronism, and loss of body potassium (measured as total exchangeable potassium).

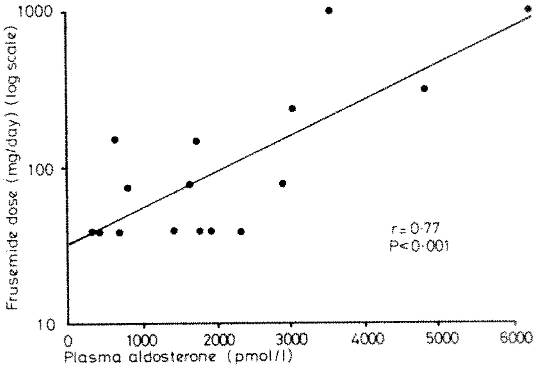

Fig. 3 *Relation of plasma aldosterone concentration to intensity of diuretic therapy expressed as daily dose of frusemide. Hyperaldosteronism is associated with intensive diuretic treatment as shown by the significant correlation ($r = 0{\cdot}77$, $P < 0{\cdot}001$).*

It may be that in severely affected patients, intensive diuretic treatment serves only to remove troublesome systemic and pulmonary oedema, reducing pulmonary vascular pressures and producing a fall rather than a rise in cardiac output in spite of clinical improvement from loss of congestion as described by Stampfer *et al.* (1968). We conclude that though the clinical condition of patients is improved by diuretic therapy, the persisting or accentuated reduction in effective arterial volume

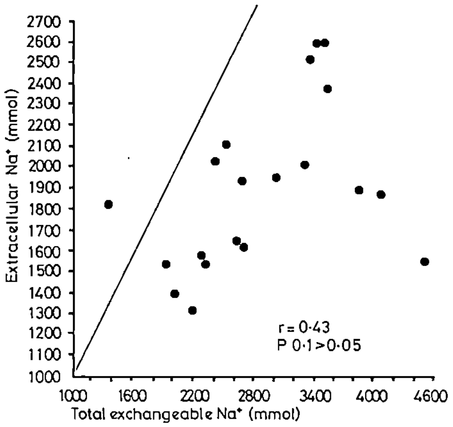

Fig. 4 *Relation of extracellular sodium to total exchangeable sodium. Extracellular sodium calculated from sulphate space and sodium concentration in plasma water is related to total exchangeable sodium (r=0·43) without statistical significance. To facilitate interpretation with the different axes the line of identity is shown. If all the body sodium is in the extracellular fluid the data should approximate to the line of identity. Deviation towards the horizontal axis indicates entry of sodium into cells so that exchangeable sodium exceeds extracellular sodium.*

leads to severe hyperaldosteronism which produces potassium depletion and may be complicated by loss of lean body mass and cardiac cachexia. In addition there is risk of a fall in intracellular potassium concentration which can precipitate fatal ventricular arrhythmias (Dreifus *et al.*, 1974). It may be that less intensive diuretic therapy would avoid the provocation of hyperaldosteronism at the expense of some residual oedema, but the relative success of operating on dried-out patients makes us hestitant to abandon this policy.

Whatever the mechanisms, whether arrhythmic or through wasting of lean tissue (Walesby *et al.*, 1978), it is possible that hyperaldosteronism and potassium depletion may contribute to the mortality of surgical treatment such as valve replacement. If operation is feasible, our surgical colleague suggests that it should be considered before hyperaldosteronism occurs, as soon as intensive diuretic treatment becomes necessary to prevent troublesome symptoms of congestion (G. Rees, 1977, personal communication).

A preliminary account of this work was presented to the joint meeting of the British Cardiac Society and the Swedish Society of Cardiology in 1975, and appears in abstract in the *British Heart Journal*, **35,** 534P; the findings are reviewed by Hamer (1977).

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Prediction of infarct size by enzymatic techniques: modification of a method and clinical application

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SUMMARY In an attempt to develop improved methods of prediction of infarct size by enzymatic methods, Shell's original algorithm has been critically evaluated in an unselected series of patients.

Poor performance of the model is partly the result of a systematic source of error associated with its mathematical formulation. A new model devoid of such limitations has therefore been developed. Residual deviations between predicted and observed CK release seem to be related to frequent and unpredictable extensions of infarction which could be verified by independent clinical, electrocardiographic, and enzymatic criteria.

The modified model may possibly be applied to the evaluation of agents aimed at limiting the spread of irreversible injury.

Prediction of infarct size from early CK data by curve fitting techniques is a potentially useful tool for the evaluation of the course of acute myocardial infarction, whether unmodified or influenced by therapeutic agents. The original algorithm was proposed in 1973 by Shell and Sobel (Shell *et al.*, 1973); it assumes a log normal distribution for CK serum activity plotted against time, and adopts a simple monocompartmental model to evaluate myocardial CK depletion as an index of the size of the infarction (Kjekshus and Sobel, 1970; Maroko *et al.*, 1971).

The fitting procedure is accomplished by a non-linear least squares computer programme, which uses data obtained during the first 7 hours or more following the initial CK rise to predict the most likely course of the entire curve. In order to estimate the expected infarct size, the projected values are subsequently analysed by the same compartmental model which is used for processing the observed data. Using this standard approach, some investigators reported good correlations between observed and predicted CK time activity curves in patients with *uncomplicated* myocardial infarction (Shell and Sobel, 1974; Morrison *et al.*, 1976; Varonkov *et al.*, 1977). On the other hand, very few data are available for a completely unselected series. Moreover, in individual cases the fit of the curve is often far from satisfactory, especially in the very early and late portions; the causes of these deviations have not been systematically analysed.

The purposes of this study were therefore: (a) to evaluate Shell's model in an unselected series of patients and, (b) to identify the sources of error associated with the model *per se*, and to distinguish them from those related to the evolution of the infarction process.

Method

The study has been carried out on 66 consecutive patients with acute myocardial infarction admitted to the coronary care unit within 6 hours of the onset of symptoms.

Blood samples were obtained hourly for the first 8 hours and then every 4 hours for 72 to 96 hours; CK serum activity was protected by 2-mercapto-ethanol 0·01 M and determined by commercial kits (Merck-1-test-CK), using Rosalki's procedure (1967).

Cumulative CK release was calculated according to Shell and co-workers (1971), by using an average value for the fractional disappearance rate of 0·001 per min. Individual *apparent* elimination rates (Ke) were also calculated from the terminal portions of the time activity curves, as suggested by Norris *et al.* (1975), except that non-linear curve fits to an exponential equation were used, thus avoiding log

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transformation and operating in the original scale (Tommasini *et al.*, 1976).

Prediction of CK curve was accomplished by Shell's method, setting limits for the index *c* as recently devised (Sobel *et al.*, 1975), to facilitate convergence of the programme. A Univac 1106 computer was used for all these and subsequent analyses.

DIFFICULTIES ENCOUNTERED WITH CONVENTIONAL PROCEDURE

Data from a preliminary series of 24 patients with the earliest CK values within the normal range (<40 IU/l), and a satisfactory fit to the log normal equation (as reflected by the ratio: overall standard error/average CK of fit points $<0{\cdot}21$) (Sobel *et al.*, 1977) were examined first. They showed that, though in uncomplicated cases the actual curve could be predicted with good approximation in its early and mid-portion, a striking deviation always occurred in the late phase, the predicted curve declining at a much slower rate. In analytical terms, while the log normal function does not decline monoexponentially, a good approximation of its rate of decay is given by the ratio (dE/dt max)/Et; this was substantially lower than the actual *apparent* elimination rate (Ke) in all cases studied. Mean figures were $0{\cdot}00061 \pm 0{\cdot}00003$ (SE) min^{-1}, and $0{\cdot}00101 \pm 0{\cdot}00004$ (SE) min^{-1}, respectively. The difference is highly significant (paired t test, $t=6{\cdot}37$ $P<0{\cdot}001$), and identifies an important source of error associated with the standard log normal approach, leading to a potential overestimation of predicted CK release. This is to be expected, since in Shell's model of compartmental analysis a slower rate of decay with respect to the Ke used in computations is equivalent to a sustained release of enzyme (Fig. 1A). Furthermore, the degree of overestimation is related to the time interval used for calculating the integral, which may result in some variability of predicted infarct size among different programmes, despite identical data.

In addition to the recognition of this potentially serious drawback, other considerations emerged from this initial study of the model.

(1) The index, *c*, estimated in the regression, nearly always coincides with either the upper or lower limit initially set, thus suggesting 'non-necessity' of the index itself.

(2) The model is applicable only to those curves with initial CK activity still in the normal range and assumes that the time of onset of CK release can be identified, which obviously applies only to a limited number of cases.

MODIFICATION OF METHOD

It must be pointed out that when a standard log normal fit to early data points is accomplished in order to predict subsequent CK time activity curve, no information is given about the expected rate of decay. It seems reasonable, therefore, that if the actual Ke could be calculated and introduced into the log normal equation, improved projections should occur.

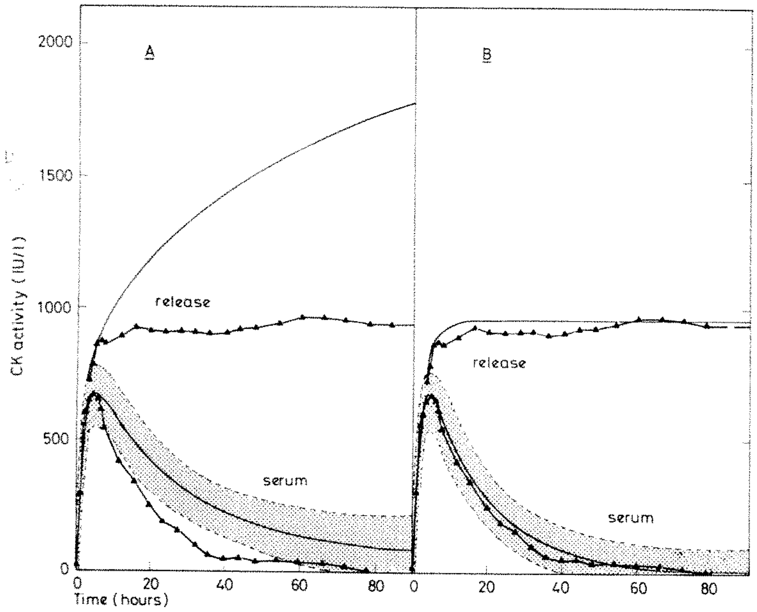

Fig. 1 *Comparison between Shell's model* (A) *and the modified model 1* (B), *applied to the same patient. In* (A) *the predicted CK time activity curve (continuous line) declines at a much slower rate than the actual (full triangles) curve. This results in a distinct and time-dependent overestimation of predicted CK release. The modified model* (B) *completely avoids this source of error, and predicted and observed CK release are very close. The dotted areas represent 95 per cent confidence limits of prediction.*

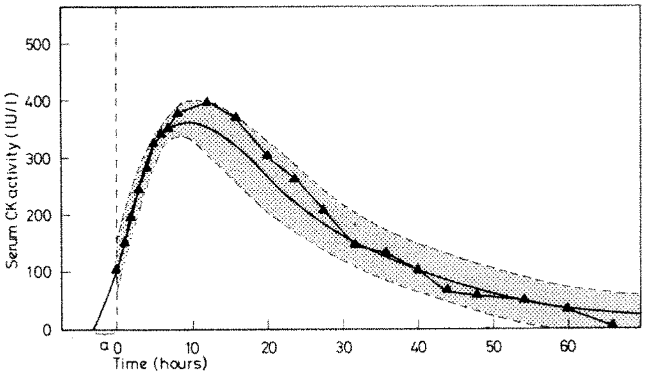

Fig. 2 *Observed and predicted CK values by the modified model 1 in an uncomplicated patient with initial values outside the normal range.* a *Represents the computer estimate of the time shift to the true 'zero time'.*

An approximation of Ke, (dE/dt max)/Et, can be obtained from the log normal equation:

$$(dE/dt\ max)/Et = \exp\,(d^4 - 1 - c)/d^4 \quad \ldots.(1)$$

by a log transformation and rearrangement of terms, if it is assumed that (dE/dt max)/Et = Ke, we obtain:

$$c = d^4 - 1 - \log d^4 - \log Ke \quad \ldots.(2)$$

The term, *c*, in the log normal equation, can be substituted by the right side of equation (2), thus reducing to 2 the number of indices to be estimated and facilitating the convergence of the programme, independently of initial guesses. This procedure does not change the shape of the curve, which is still log normal. It does, however, restrict the fitting process to a subset of curves, whose rate of decay closely approximates Ke (Fig. 1B).

The model is further modified by adding a new index, *a*, as a time shift, to allow for possible uncertainty about real 'zero time'. This results in increased flexibility, allowing mathematical analysis to be performed even when initial values are already outside the normal range (Fig. 2).

The final function used to fit the CK time activity curves now assumes the form:

$$Y = [b/(t+a)] \times \exp\,[-(\log(t+a) - d^4 + 1 + \log d^4 + \log Ke)^2/2d^4] \quad \ldots.(3)$$

Results

(a) CONFORMITY OF MODIFIED MODEL TO PATIENTS' DATA

This was assessed in a group of 30 patients with an uncomplicated course, as reflected by absence of recurrent chest pain or other evidence of extension. By using equation (3) and the corresponding partial derivatives, a non-linear fit was performed with a BMDX 85 program (Dixon, 1970), in each case using all data points after baseline subtraction, and introducing individual/previously calculated Ke. In those cases where initial CK activity was above 40 IU/l, this value was subtracted; no limits were used. In the modified model, predicted CK release can be calculated through the indefinite integral, that is, independently of the time interval, from the following relation:

$$\text{Predicted CK release/ml} = 2 \times b \times d^2 \times Ke \quad (4)$$

In the present series, the correspondence was very close between CK release calculated from actual data and that obtained from curve fits, suggesting that the transformation of the log normal equation did not worsen the model for the process of fitting. The regression equation was:

$$\text{Observed CK release} = 1{\cdot}03 \text{ predicted CK release} - 0{\cdot}8 \ (n = 30,\ r = 0{\cdot}9994).$$

Since some limits for the time shift index, *a*, were found to be necessary when employing the model in predictions from early data, they were set as +3, and 0·001 hours, by assuming a mean delay of about 3 hours from onset of symptoms (in our patients within 6 hours before 'zero time'), to initial CK release. These limits were also consistent with the average value of *a*, previously obtained when using all data points in the group of uncomplicated patients ($a = 2{\cdot}29 \pm 1{\cdot}82$ hours).

The time shift index, *a*, was set equal to zero only in those cases where the actual onset of CK release could be precisely identified.

(b) PREDICTION OF CK TIME ACTIVITY CURVES IN RANDOMISED SERIES OF PATIENTS

This was accomplished by a non-linear least squares fit to data collected over an interval of 7 hours after initial CK rise, arbitrarily defined as greater than 3 IU/l over baseline levels. A wholly randomised series of 66 consecutive patients was analysed. Excluded from the study were only patients submitted to closed chest massage and electrical countershock, or those who died before CK activity returned to baseline levels. Intramuscular injections were avoided, as well as other potential sources of error such as plasma volume manipulations or administration of drugs known to inhibit the activity of the reticuloendothelial system. Moreover, extracardiac sources of total plasma CKs were excluded in each case by CK isoenzyme analysis.

Shell's model of prediction was applied only to those cases ($n=59$) with initial CK values still in the normal range, as suggested by the authors. With this model the integral was evaluated at 48, 72, and 96 hours; since a subsequent analysis disclosed that overall best performances were attained at 48 hours, we referred to this time interval for further comparisons.

With this modified model, two different approaches were adopted. In the first case, individual/previously calculated Ke was introduced into the log normal equation, thereby assuming cessation of enzyme release during the monoexponential portion of the curve (modified model 1). In the second case, an average value for Ke (0·001/min) was used. This represents merely the information available about the expected rate of decay, and is independent of any assumption about the rate of release of the enzyme (modified model 2).

Predicted cumulative CK release was obtained through the indefinite integral, as described in paragraph (a).

The results are summarised in Table 1.

The performance of all the 3 models of prediction seemed to be poor, even though the correlation coefficient of the modified model 1 was found to be significantly higher than Shell's one. We considered that one of the reasons for the unreliability of the methods of 'prediction' of CK curve might consist in the 'unpredictability' of the natural course of the infarction, with particular reference to the very frequent occurrence of extensions, as judged from a clinical standpoint.

Table 1 *Correlations between observed (Obs CKr) and predicted (P_2 CKr) CK release in an unselected series of patients*

Model	*Regression equation*	*Correlation coefficient*
Shell	Obs CKr $=$ 0·88 $\pm$ 0·16 P_2 CKr $+$ 1040 $\pm$ 330 (SD)	$r=0·59$ $n=59$
Model 1 (ind. Ke)	Obs CKr $=$ 0·85 $\pm$ 0·08 P_2 CKr $+$ 778 $\pm$ 190 (SD)	$r=0·81$* $n=66$
Model 2 (aver. Ke)	Obs CKr $=$ 0·87 $\pm$ 0·12 P_2 CKr $+$ 922 $\pm$ 257 (SD)	$r=0·68$ $n=66$

* Statistically significant with respect to Shell.

Table 2 *Correlations between observed (Obs CKr) and predicted (P_2CKr) release in patients without (nonext) and with (ext) extension of infarction*

Model	*Regression equation*	*Correlation coefficient*
Shell		
Nonext	Obs CKr $=$ 0·98 $\pm$ 0·20 P_2 CKr $+$ 533 $\pm$ 453 (SD)	$r=0·65$ $n=35$
Ext	Obs CKr $=$ 1·00 $\pm$ 0·29 P_2 CKr $+$ 1325 $\pm$ 478 (SD)	$r=0·59$ $n=24$
Model 1 (ind. Ke)		
Nonext	Obs CKr $=$ 0·90 $\pm$ 0·04 P_2 CKr $+$ 168 $\pm$ 120 (SD)	$r=0·96$† $n=38$
Ext	Obs CKr $=$ 1·54 $\pm$ 0·19 P_2 CKr $+$ 541 $\pm$ 304 (SD)	$r=0·85$ $n=28$
Model 2 (aver. Ke)		
Nonext	Obs CKr $=$ 0·84 $\pm$ 0·05 P_2 CKr $+$ 273 $\pm$ 120 (SD)	$r=0·95$† $n=38$
Ext	Obs CKr $=$ 1·59 $\pm$ 0·23 P_2 CKr $+$ 720 $\pm$ 385 (SD)	$r=0·79$ $n=28$

† Highly significant with respect to Shell.

Covariance analysis (nonext versus ext)

Model	*F value*	*P value*
Shell	5·33	0·025
Model 1	54·9	1×10^{-9}
Model 2	48·7	2×10^{-9}

We therefore selected patients with evidence of extension indicated by at least 2 of the following criteria: (1) recurrent heavy chest pain, presumably not pericardial in origin (clinical extension); (2) appearance of new Q waves in different sites with respect to initial electrocardiographic abnormalities (electrocardiographic extension); (3) the presence of secondary peaks or well-defined flexi (through 5 or more points) in the CK time activity curve (enzymatic extension) (Fig. 3).

On this basis, 2 subsets of patients could be identified (Fig. 4). In our series, the overall incidence of extensions was 40 per cent; this value agrees with that reported by others (Reid *et al.*, 1974; Mathey *et al.*, 1975).

(c) PREDICTIONS IN PATIENTS WITH AND WITHOUT EVIDENCE OF EXTENSION

When all patients with extensions were excluded, striking differences emerged among the different models in terms of performance. As can be seen in Table 2, as well as in Fig. 4, predictions by Shell's model were not substantially improved. Instead, very good correlations were found between calculated CK release and predicted values for both the modified model 1 and 2.

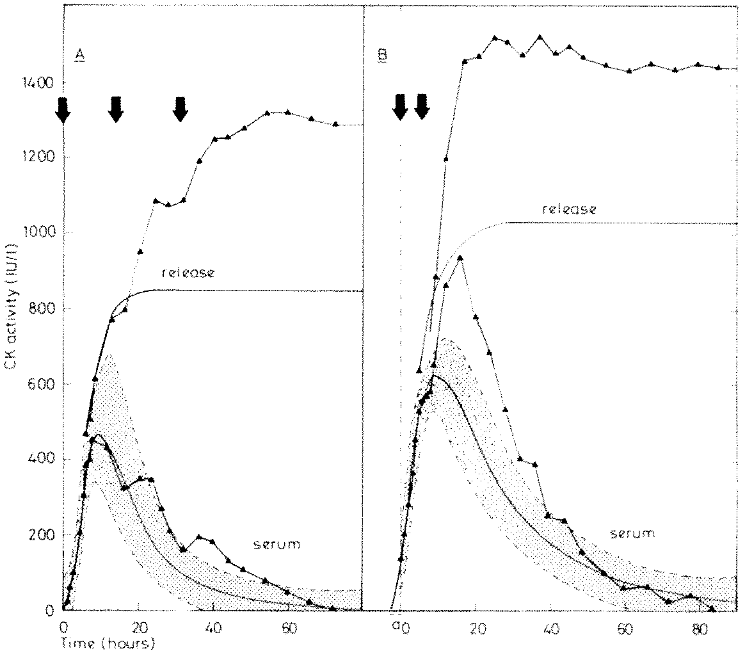

Fig. 3 *Time course of CK serum activity in 2 patients with clinical evidence of extension of the infarction. The arrows indicate episodes of severe chest pain, which is followed by secondary peaks* (A), *or flexi* (B), *probably reflecting an increase in myocardial damage.*

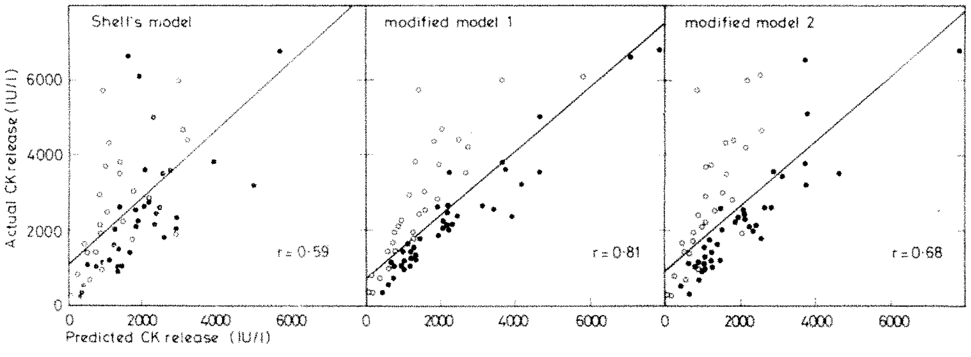

Fig. 4 *Correlations between observed and predicted CK release in an unselected series of patients. The open circles indicate cases with clinical or electrocardiographic evidence of extension; closed circles represent 'unextended' cases.*

Significant correlations were also found for the group of patients with extension of infarction, though the actual CK release was substantially underestimated.

We looked for significant differences between regression lines obtained in the groups with and without extension of infarction by means of covariance analysis applied to each of the prediction models. The hypothesis of the existence of two different populations, as defined through independent clinical, electrocardiographic, and enzymatic criteria, could be verified for both the modified models 1 and 2.

This was not true of Shell's model, which was much less precise in distinguishing between cases with and without extension. This conclusion was also verified by a linear discriminant function analysis, by which 31 per cent of patients were incorrectly classified as extended or unextended by Shell's model, compared with 9 and 14 per cent by the modified models 1 and 2, respectively.

Discussion

It is well recognised that Sobel's method for estimation of infarct size by enzyme analysis has limitations (Roe and Starmer, 1975), especially when applied to man, because of uncertainty about the values of the indices of the model.

Some information is contained in a recent study (Tommasini *et al.*, 1978) based on reinfusion of autologous plasma harvested CK in 6 patients with acute myocardial infarction; this shows a main distribution space of 3314 ± 146 (SD) ml, which closely approximates to plasma volume, and a disappearance rate of $0{\cdot}002 \pm 0{\cdot}0006$ (SD) min^{-1}.

Although the ratio of CK released to CK depleted from the heart is very difficult to calculate in man, the results obtained by Bleifeld *et al.* (1977) suggest that it might be similar to that observed in the experimental animal.

Besides these observations it must be stressed that CK projections are not dependent on the indices of the compartmental model, but only on the mathematical formulation of the algorithm and on the CK values used in the fitting procedure.

The present study was dictated by the following considerations:

(1) Though Shell's algorithm was initially regarded as potentially useful in the clinical setting, inconclusive or contradictory results have been reported, concerning both the accuracy of the method for predicting CK time activity curve in unselected series, as well as for evaluating the effect of some pharmacological measures aimed to protect the ischaemic myocardium (Morrison *et al.*, 1976; Roberts *et al.*, 1976; Sobel *et al.*, 1977).

(2) Data from a preliminary study suggested that a systematic source of error was associated with the mathematical formulation of the algorithm, leading to a random degree of overestimation of predicted CK release.

(3) The model appeared to be applicable only to those cases in which the earliest CK values had not risen above the normal range.

The purpose of this study was therefore to develop a new model having none of these limitations, and to compare it critically with the original algorithm in a completely unselected series, as well as in patients with and without evidence of extension of the infarction, as determined by independent criteria.

It was shown that, in an unselected series, the ultimate CK release cannot be predicted by any of the models because of the frequent and unpredictable occurrence of extension of infarction. However, the modified models could accurately predict CK time activity curves in 'non-extended' patients. The prediction gives valuable early prognostic information, and helps in recognising deviations from the normal pattern which may be caused by late extension.

It could be argued that an increase of the rate of release of the enzyme could paradoxically reflect an augmentation of coronary flow, which is a favourable phenomenon. However, the strong association between independently determined evidence of extension and an increase in the rate of CK release suggests that this explanation is unlikely.

This view is also supported by some recent experimental work (Varonkov *et al.*, 1977), in which an increase in coronary flow led to only transient quantitatively insignificant spikes of CK release.

It must be recognised that a serious limitation of Shell's algorithm, namely the delay of 7 hours required for data acquisition before any therapeutic measure can be implemented, is still present in the modified models. Many investigators believe that the bulk of cell death occurs in the first hours after coronary occlusion. If this were true, only therapeutic treatments started very early after the onset of symptoms could be effective in reducing the size of the infarction. On the other hand, if the rate of release of CK is an index of the evolution of the infarct, as indicated by some histochemical and electrophysiological studies (Cox *et al.*, 1968; Tommasini *et al.*, 1976; Inoue *et al.*, 1977), a substantial proportion of myocardial cells may be salvageable as late as 12 to 24 hours after coronary occlusion. This applies particularly to cases with evidence of extension or where a self-perpetuating cycle of cell damage is likely to occur, as in congestive heart failure or in cardiogenic shock (Gutovitz *et al.*, 1978). In this setting, our modified methods for prediction of CK time activity curves could be especially useful for evaluating therapeutic agents aimed at preventing the spread of irreversible injury.

The improved performance of the modified models is probably because more information is used, at the same time avoiding the use of unnecessary indices and limits. The introduction of a time shift results in increased flexibility, allowing the algorithm to be used in all cases.

The modified model 1 was based on the hypothesis that the true elimination rate could be calculated from the terminal portions of CK time activity curves. This, however, is not supported by recent experimental work in dogs (Sobel *et al.*, 1978) as well as in man (Tommasini *et al.*, 1978) after reinfusion of autologous CK.

Practical considerations, therefore, suggest the use of the modified model 2, in which average values for Ke are used. This eliminates any assumption about the real elimination rate of CK, and is more in keeping with the concept of prediction.

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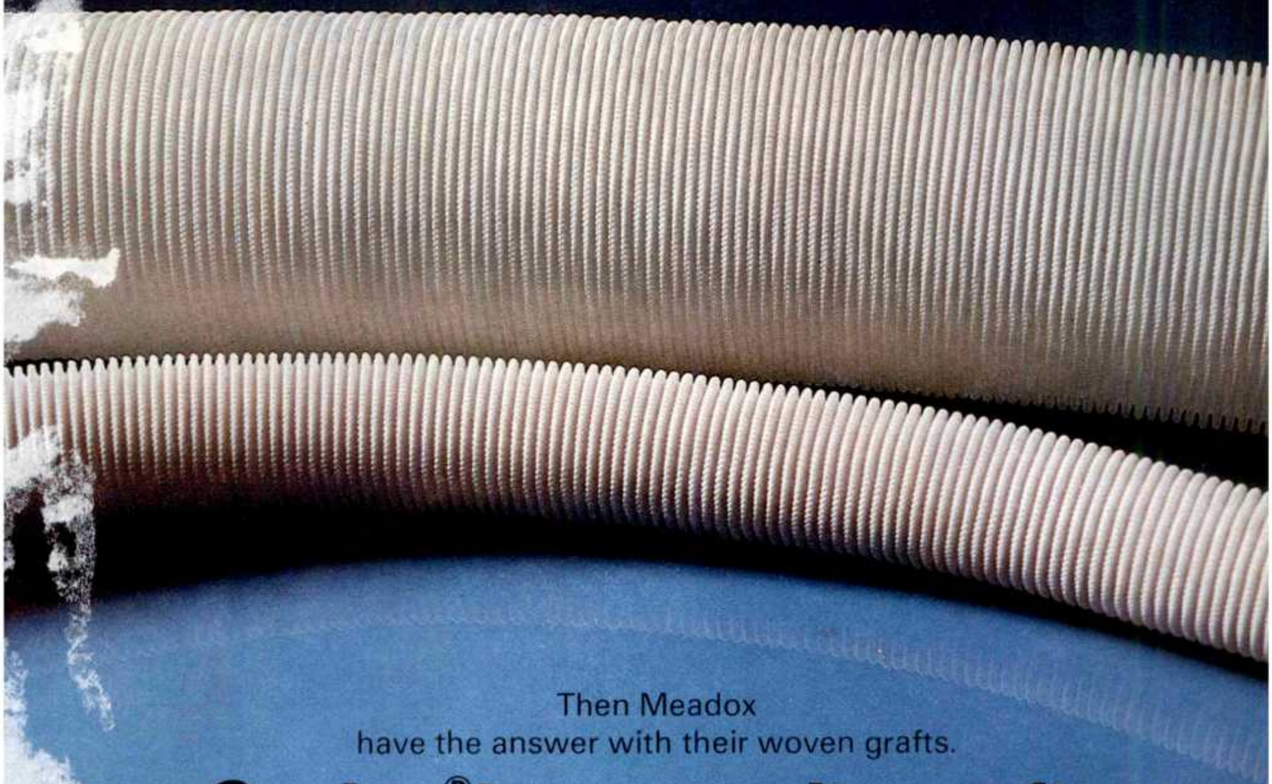

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Reoperation for recurrent angina

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SUMMARY Forty patients with persistent or recurrent angina after an aortocoronary bypass procedure underwent a second operation. The cause of recurrent angina, defined by angiography, was thought to be isolated graft failure in 13 patients, progression of disease in ungrafted vessels in 4, incomplete revascularisation in 2, and stenoses distal to patent grafts in 1. More than one factor was responsible in 20 patients.

There was 1 early postoperative death and 3 perioperative myocardial infarctions. Thirty-four patients have been followed for more than 3 months (4 to 63 months). Of these, 17 had previously bypassed vessels regrafted and 5 are symptom free, 4 have mild angina, and 8 have severe angina. Ten patients had previously ungrafted vessels grafted and 4 are symptom free, 3 have mild angina, 2 have severe angina, and 1 is limited by breathlessness. Seven patients had a combined procedure and 4 are symptom free, 1 has mild angina, and 2 have severe angina.

Reoperation can be carried out safely but the results are less satisfactory than for a primary procedure.

tocoronary bypass surgery abolishes or improves
na in most patients (Cooley *et al.*, 1973; Assad-
ell *et al.*, 1975; Donaldson *et al.*, 1978). In
however, the operation is unsuccessful, while
rs angina recurs after an initially good result.
e large number of such operations currently
rried out in the United Kingdom, this
with persistent or recurrent angina
an increasingly large number of patients.
n be managed satisfactorily with conserva-
ures, but in some cases intractable symp-
sent a difficult therapeutic problem and a
operation has to be considered. This paper
ibes our experience with 40 second myocardial
ascularisation operations carried out at the
ndon Chest Hospital since 1973.

atients

he 40 patients, 37 men and 3 women aged
ween 34 and 66, had all had a coronary artery
ss operation; patients with a previous Vineberg
ure are not included. Nine had had a single
21 a double graft, 9 a triple graft, and 1 a
ple graft. Saphenous vein had been used as
nduit in all cases except for 1 in which the
al mammary artery had been implanted.
terectomy was employed in addition to grafting in 7 patients on a total of 13 arteries. One patient had had a left ventricular aneurysm excised in addition to grafting.

Angina recurred from the early postoperative period (that is as soon as the patient was sufficiently mobile to develop effort angina) up to 54 months after operation. It was graded in severity on a scale of 1 to 4, in which grade 1 is angina occurring only with severe exertion, grade 2 is angina during normal activities, grade 3 is angina with minimal exertion or provoked by emotional disturbances, and grade 4 is angina at rest. At the time of the second operation 9 patients had grade 2 angina, 20 had grade 3, and 11 grade 4.

CAUSE OF RECURRENT ANGINA

Selective graft and coronary angiography was carried out to determine the state of grafts and of native coronary circulation. Left ventricular function was assessed from a single plane (RAO) left ventriculogram: ejection fraction was determined by the area-length method (Sandler and Dodge, 1968) using a planimeter, and the 3 wall regions (anterior, apical, and inferior) were described as showing normal or abnormal movement in systole. The findings were compared with the preoperative angiogram.

The causes of recurrent or persistent angina, occurring singly or in combination, were identified

d for publication 1 February 1979

as occlusion or stenosis of one or more grafts ('graft failure'), the persistence of significant narrowings in major ungrafted vessels ('incomplete revascularisation'), the development of new stenoses or occlusions in major ungrafted arteries ('progression of disease'), and the presence of occlusion or stenosis beyond the distal anastomosis of patent grafts. In the last group it was usually difficult to judge whether the graft had been placed too proximally or whether disease had progressed since operation, particularly in those in whom the grafted vessel was occluded on the preoperative angiogram.

In 13 patients graft failure alone was thought to be the cause of recurrent angina, 2 were judged to have had an incomplete first operation, and 4 had satisfactory grafts but new disease in major ungrafted vessels. One patient's poor result was attributable solely to the presence of severe stenoses distal to the insertion of 2 of his 3 grafts. Nine patients had graft failure combined with an incomplete first operation, 8 had a combination of graft failure and new disease, and 2 had graft failure in association with disease distal to patent grafts. One patient (case 24) had an incomplete first operation and in addition a new stenosis in an ungrafted artery and disease distal to an otherwise satisfactory graft.

With 1 exception, all patients with an incomplete first operation, alone or in combination with other factors, developed recurrent angina within a year. The single late recurrence was in a patient (case 24) who, in addition, had stenoses distal to a patent graft and progressive disease. One patient (case 34) had an occluded graft plus disease in 2 vessels which it had not been thought feasible to graft at the first operation; he had continued to have mild angina for 30 months and then abruptly deteriorated. Since the native circulation had not changed it was concluded that late graft occlusion was responsible for his recurrent severe symptoms. Patients with progressive disease developed recurrent angina as early as 3 months after operation. In patients with graft failure angina recurred from the early postoperative period up to 42 months after operation.

In 1 patient (case 23) left ventricular function before the second operation was better than before the first: a region of akinesia in relation to a blocked anterior descending artery contracted normally in the presence of a satisfactory graft. The patient who had a left ventricular aneurysm excised at the first operation (case 38) had an almost identical ejection fraction before the second. In 6 patients left ventricular function had deteriorated since the first operation with the development of new regions of abnormal wall motion. This was related to blocked or narrowed grafts in 4 patients (1 of whom had a left ventricular aneurysm) and to a diseased ungrafted artery in 2. Four patients (excluding the one with an aneurysm) had an ejection fraction of 40 per cent or less; in 1 it was 25 per cent. Ten patients had normal left ventricular function at the time of the second operation, 26 had 1 area of abnormal wall motion, and 4 had more than 1 abnormal region. None had significant mitral regurgitation.

Four patients had diabetes mellitus, 5 were receiving treatment for hypertension, and 13 admitted to smoking more than 10 cigarettes a day up to the time of the second operation. Determination of fasting blood lipids and lipoprotein electrophoresis were carried out in 28 patients. Hyperlipoproteinaemia was detected in 10: 4 had type IIA (Fredrickson), 2 type IIB, and 4 type IV.

SURGICAL TECHNIQUE

The average time between the first and second operations was 22·7 months and ranged from 6 to 72 months.

Reoperation was done using cardiopulmonary bypass in 39 patients; in 35 this was combined with intermittent ischaemic arrest (ventricular fibrillation and aortic cross-clamping) allowing the temperature to drift down to 30°C. In 4 patient
hypothermic arrest was produced by perfusion o
the aortic root with cold Hartman's solution
patient the only procedure was the in
bypass graft between the aorta and a
and cardiopulmonary bypass was
Aortic cannulation was used routi
patient emergency femoro-fem
established after the division o
anterior descending artery w
being opened.

In 17 patients (cases 1 to 17) the o
was regrafting of previously grafted
revision of existing grafts. Twenty-thr
grafts were implanted, 3 grafts with n
distal anastomosis ('snake grafts'), an
between the aorta and an existing graft o
its proximal end. In 1 patient arm vein
used; suitable leg vein was found for all the
Endarterectomy was carried out on 8 arter
in 2 of these the vessel was closed with a vein
as well as a graft. Thirteen patients (cases 18
had grafts placed to previously ungrafted
A total of 17 vessels were bypassed and e
tomy was carried out on 3. One patient
group had an anteroapical left ventricular
excised in addition to grafting. T
(cases 31 to 40) had combined procedur
both regrafting of or revision of grafts
grafted vessels and the bypassing of arte

first time. A total of 22 grafts were implanted in this group, including 1 snake graft. Endarterectomy was carried out on 5 vessels. In 1 patient in this group it was possible to reimplant the top end of a graft which had occluded at the proximal anastomosis.

Discrepancies between the cause of recurrent angina diagnosed angiographically and the actual operation carried out on certain patients are explained by the fact that it was not always possible to graft or regraft vessels with severe diffuse disease, and in 1 patient an apparently large stenosed circumflex artery could not be found.

SURGICAL COMPLICATIONS

There was one early postoperative death from left ventricular failure and necropsy showed widespread infarction of the left ventricle. This patient had severely impaired myocardial function before the second operation (ejection fraction 25%) and required extensive endarterectomy. Of the 39 survivors, 3 had definite electrocardiographic evidence of perioperative myocardial infarction in the form of new Q waves: one was the patient whose left anterior descending graft was divided during exposure of the heart. None of the patients had to return to the operating theatre for control of excessive postoperative bleeding.

[illegible] reoperation

[illegible]t details of the first operation, the [illegible]rrent angina, the procedure at the [illegible] and follow-up of each patient are [illegible]

M: [illegible] had their second operation within tive meas [illegible] months, and though none has developed toms pr [illegible] angina it is clearly too soon to make a second [illegible]essment of the result; they have there- desc [illegible] excluded from further analysis. The rev [illegible] 34 survivors had their operation between L [illegible] months ago; follow-up is complete to [illegible]8.

P [illegible] have been no late deaths or documented [illegible]ardial infarctions. Only 13 patients are [illegible] free. A further 8 are reasonably satisfied [illegible] their result in that though they still have [illegible], it occurs only with unusual exertion (grade [illegible] of the patients who had a perioperative [illegible]dial infarction (case 22) has no pain but is [illegible] by breathlessness on exertion. Twelve [illegible] continue to suffer from severe angina.

[illegible] results of each main type of operative [illegible] are given in Table 2. Of the 17 patients [illegible] previously grafted vessels were revised Rece [illegible]ation was of no benefit in 8. Five are symptom free and 4 have mild angina. By contrast, 7 of the 10 patients who had grafts to previously ungrafted vessels and 5 of the 7 who had a combined procedure were improved by their second operation, with 8 symptom free and a further 4 with only mild residual angina.

Eight patients with angina, which was persistent or recurrent after a second operation, have been recatheterised. Five out of 10 grafts into previously grafted vessels were found to be occluded and the 5 patent grafts are all unsatisfactory with poor peripheral run-off. All 5 grafts to previously unbypassed vessels remain patent, though 1 has a poor run-off and another, in a patient whose first operation was incomplete (case 19), has no peripheral run-off at all as a result of occlusion of the artery at the site of anastomosis; this patient also has an important vessel with a major proximal stenosis which was left ungrafted at both operations. One patient with persistent pain has 4 patent grafts and the cause of his recurrent symptoms is not understood. All the grafts in 1 patient (case 13) have occluded and he has undergone a third operation, again without relief of his angina.

Discussion

The difficulties of a second heart operation are well known and relate mainly to the problems of exposure and haemostasis resulting from adhesions from the first procedure. Our experience indicates that this need not cause an unduly high complication rate. In only 1 patient did morbidity result directly from the difficult exposure when his functioning left anterior descending graft was divided; he had an infarct despite the institution of emergency cardiopulmonary bypass and repair of the damage. The mortality (1 out of 40) is close to that which can be achieved with a first operation and the single death was related perhaps more to the type of operative procedure (extensive endarterectomy in the presence of an already poorly functioning ventricle) than to the fact that it was the patient's second bypass operation.

Overall, the long-term results are disappointing, with a third of the patients followed for more than 3 months deriving no benefit from the second procedure and only a third symptom free. In particular patients in whom the only identifiable cause of recurrent angina was failure of previous grafts did badly. Similar results were reported after 21 reoperations carried out at Stanford University (Winkle *et al.*, 1975). It is easy to understand that if a technically skilful first operation is followed by graft occlusion the same factors which caused the primary failure will militate against a successful

Table 1 *Details of patients*

Case no.	*Age (y)*	*First operation*	*Recurrent AP*		*Cause of recurrence*	*Second operation*	*Follow-up*	*Angina grade*	*Comments*
			Time	*Grade*					
1	53	Inf. LV, LCx LAD grafts	3/12	3	All grafts occl.	LAD, RCA grafts RCA-PDA LAD end.; vein patch LAD	30·12	3	Unable to regraft Cx
2	49	RCA LCx LAD grafts; LAD end.	3/12	3	Cx graft occl. distal LAD occl.	Distal LAD graft	21/12	3	Unable to regraft Cx
3	43	LAD LCx grafts; LCx end.	14/12	3	All grafts occl.	LAD graft	15/12	4	Unable to regraft Cx
4	56	RCA LAD LCx grafts	4/12	3	LAD graft occl. proximally	Graft to LAD graft	4/12	0	
5	43	LCx LAD grafts	6/12	4	Cx graft occl.	LCx graft	9/12	0	
6	35	LMCA RCA LCx grafts; LMCA LAD RCA PDA LCx end.	2/12	2	Stenosis distal to RCA and LCx grafts	LAD distal RCA and LCx grafts	16/12	2	Reinvestigation: poor run-off from all grafts
7	64	PDA LAD LCx grafts	1/52	2	LAD and PDA grafts occl.	RCA-PDA snake, LAD graft	10/12	1	Poor vein first op.; arm vein second op.
8	58	RCA LCx grafts	3/12	3	Cx graft occl. RCA graft stenosed	LCx RCA grafts	12/12	1	
9	47	LAD PDA grafts	2/12	2	Both grafts occl; old LCx stenosis	RCA LAD grafts; RCA LAD end.; LAD vein patch	33/12	1	Poor vein first op.; unable to graft Cx
10	57	RCA LAD AVCx grafts; diagonal end.	24/12	4	RCA and Cx grafts occl.; stenosis distal LAD	RCA graft	11/12	0	
11	58	RCA diagonal grafts	22/12	4	RCA graft stenosis	Graft to RCA graft	27/12	0	Cardiopulmonary bypass not req.; ? stenosis due to fibrosis where RA appendage excised
12	63	RCA LAD LCx grafts; RCA and LCx end.	12/12	3	RCA and LAD grafts occl.	RCA LAD grafts	6/12	0	Poor LV—EF 30%
13	62	RCA LCx grafts	25/12	3	Both grafts occl.	RCA graft MCx-LCx snake RCA MCx end.	25/12	4	Reinvestigation: all grafts occl.; third op. no improvement
14	66	RCA LAD LCx grafts	5/12	3	All grafts occl.	RCA LAD LCx grafts. RCA LCx end.	8/12	1	Poor vein at first op.
15	65	LAD LCx grafts	5/12	3	Both grafts occl.	LAD-LCx snake	10/12	3	
16	49	LAD graft	2/52	4	Graft occl.	LAD graft	30/12	3	Reinvestigation: graft occl.
17	38	RCA LAD LCx grafts	1/12	3	RCA and LCx grafts occl.	PDA LCx grafts	10/12	2	Reinvestigation: poor run-off from new grafts
18 (F)	45	RCA LCx grafts	6/12	3	New stenosis LAD	LAD graft	12/12	0	Perioperative anterior infarct
19	43	LAD graft	1/52	3	Old first LCx stenosis and third LCx occl.	3LCx graft and end.	6/12	2	1LCx not grafted; reinvestigation: 3LCx occl. distal to graft
20	52	LAD graft	10/12	3	New stenosis RCA and PDA	RCA graft	29/12	1	
21	40	LAD graft	3/12	3	Old RCA and LCx stenosis	RCA graft	63/12	1	LCx not grafted
22	49	LAD LCx grafts	42/12	2	Progression RCA stenosis	PDA graft	9/12	0	LAD graft accidentally divided; anterior infarct grade 2 dyspnoea

Table 1—*continued*

Case no.	*Age (y)*	*First operation*	*Recurrent AP*		*Cause of recurrence*	*Second operation*	*Follow-up*	*Angina grade*	*Comments*
			Time	*Grade*					
23	50	LAD PDA grafts	2/12	3	PDA graft occl.; old stenoses AVCx and LCx	AVCx graft and end.	39/12	2	Reinvestigation: poor run-off from Cx graft
24	42	LAD IM graft LCx graft	24/12	2	New stenosis RCA; stenosis distal to LCx graft; old stenosis 3LCx	RCA graft and end.	35/12	1	Unable to regraft 1LCx or find 3LCx; reinvestigation: poor run-off LCx and RCA grafts
25	57	LAD diagonal grafts; LAD diagonal end.	12/12	4	Diagonal graft occl.; progressive stenosis RCA and Cx	PDA and AVCx grafts	22/12	0	EF 35% before second operation
26	56	LAD graft	7/12	3	LAD graft occl.; old LCx stenosis	LCx graft	30/12	0	LV aneurysmectomy at second op.
27	34	LAD graft	4/12	3	LAD graft occl.; progressive stenosis RCA and LCx	PDA and LCx grafts	43/12	0	LAD too small to regraft
28	58	LAD graft	3/12	3	Progression RCA and LCx	RCA and LCx grafts	4/52	0	
29	54	LAD LCx grafts	54/12	2	LAD graft occl.; new RCA occl.	RCA graft	4/52	0	New inferior akinesia since first op.; unable to regraft LAD
30	58	LAD LCx grafts LAD end.	4/12	4	LCx graft occl.; old 2LCx stenosis	1LCx and 2LCx grafts	4/52	0	
31	60	LAD and PDA grafts	1/52	3	LAD graft occl.; ungrafted LCx	LAD LCx grafts, LAD LCx end.	24/12	2	Low flow LAD graft first op.
32	57	RCA LCx grafts	42/12	2	Both grafts occl.; progression LAD	RCA LCx LAD grafts	7/12	0	
33	53	RCA LAD grafts	1/52	4	LAD graft occl.; ungrafted LCx PDA	LCx PDA LAD grafts	43/12	1	
34	57	1LCx graft	30/12	3	LCx graft occl.; ungrafted LAD and 2LCx	LAD 2LCx grafts, 2LCx end.	25/12	0	
35 (F)	53	LAD LCx grafts	18/12	2	LCx graft occl.; progression RCA	RCA graft; re-implant LCx graft	12/12	0	LBBB
36	44	LAD graft	1/52	4	LAD graft occl.; ungrafted LCx RCA	PDA LAD grafts, PDA LAD end.	—	—	EF 25% before second op.; died postop.; LCx not grafted
37	48	RCA LAD grafts	42/12	4	LAD graft occl.; progression LCx	LAD LCx grafts	12/12	0	EF 40% before second op.; new apical akinesia
38	44	PDA LCx grafts LV aneurysmectomy	8/12	2	LCx graft occl.; progression LCx and diagonal	1LCx 2LCx diagonal grafts	21/12	4	Reinvestigation: all grafts patent
39	55	1LCx 2LCx LAD grafts	3/12	4	Cx grafts occl.; LAD graft stenosis; new RCA stenosis	RCA 1LCx grafts	4/52	0	LAD not regrafted
40 (F)	57	LAD RCA grafts	1/12	4	RCA graft occl.; ungrafted LCx	PDA-inf LV snake LCx graft	4/52	0	

Abbreviations: LMCA, left main coronary artery; RCA, right coronary artery; PDA, posterior descending coronary artery; Inf. LV, left ventricular branch of RCA (not PDA); MCx, main circumflex artery; AVCx, atrioventricular branch of circumflex artery; LCx, lateral circumflex artery (numbered 1 to 3); end., endarterectomy; occl., occluded; IM, internal mammary graft; LV, left ventricular; EF, ejection fraction. All patients male except when specified (F).

Table 2 *Late results of each type of operative procedure*

	Symptom free	*Mild angina*	*Severe angina*	*Total*
Re-do SVG	5	4	8	17
New SVG	4	3	2	10*
Combined procedure	4	1	2	7

* One patient in this group had grade 2 dyspnoea.
SVG, saphenous vein graft.

second attempt. Such factors were identified in surprisingly few cases.

In 1 patient proximal stenosis in a graft seemed to be related to fibrosis at the site of the amputated right atrial appendage, and in 3 the vein was noted to be of poor quality. One patient with a severely diseased distal left anterior descending artery had a low flow down his graft before the chest was closed, but in the others the first grafts seemed to have been executed without difficulty.

By contrast, patients in whom the second procedure included the grafting of previously undisturbed vessels did rather better. Seven out of 10 in whom this was the sole procedure were improved, and in 1 of the failures it is clear that a 'target vessel' was not grafted. Five out of 7 patients who had combined procedures with grafts placed both to previously grafted and to previously ungrafted arteries were improved by the operation and the cause of recurrent pain in 1 of them is obscure because reinvestigation has shown the presence of 4 satisfactory grafts.

Two hundred and nineteen reoperations have been reported from the Cleveland Clinic (Irarrazaval *et al.*, 1977). Their long-term results are rather better than those reported here, with 65 per cent of patients asymptomatic 2½ years later. These excellent results may be explained in part by the inclusion of 87 patients who had had a previous Vineberg operation so that none of their diseased arteries had been grafted, but this cannot be the complete explanation because the outlook was equally good whether the second procedure was for graft failure, progressive disease, or combined factors. Many of the American patients were referred from other centres and it is possible that the surgeons who carried out the first operation tended to be less experienced than those who did the second, so that there were correctable technical factors in a higher proportion of cases than in the patients described here. The fact that the operative mortality and the incidence of perioperative infarction are similar in both series gives some support for this view.

Our results show that a second aortocoronary bypass operation can be carried out safely. More experience is required before firm guidelines on the indications for reoperation can be drawn, but even at its worst a 50 per cent improvement rate in patients with isolated graft failure may be considered to justify a second attempt in the face of intractable angina and the low operative mortality which can be achieved.

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A cardiac conduction monitor and probe for intraoperative identification of conduction tissue

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don

SUMMARY Intraoperative identification of the atrioventricular conduction tissues is essential in some cases of complex congenital heart disease. In using such monitors, difficulties may arise with display and interpretation of the recorded signal, with the maintenance of sinus rhythm, and with the need for a second observer. In this paper we describe the design and construction of a simple monitor which incorporates the following: an atrial pacing module so as to ensure unchanged anterograde conduction to the ventricles and thus avoid changes in PR interval and QRS complex which may occur with surgical manipulation or hypothermia; an audible click which allows the surgeon to confirm capture and an error light which indicates arrhythmias or loss of pacing; an oscilloscope with a 25 mm/s sweep which displays the electrocardiogram and a 650 mm/s sweep for the conduction signal; a variable time width window triggered by the atrial pacing stimulus which is set to occur during the isoelectric PR segment allowing artefact outside this range to be excluded; and a tripolar electrode probe which detects conduction tissue signals whose absolute magnitude is summed to give a single signal. This is also displayed on the oscilloscope and is used to trigger an audible tone and to flash a lamp. The indicator is muted should atrioventricular dissociation or artefact occur during monitoring. The instrument has simplified intraoperative identification of the atrioventricular conduction system and reduced the need for d observer.

ion of specialised atrioventricular issue in patients with some forms of ongenital heart disease makes the intra- ive identification of these tissues desirable n contemplating corrective surgery. Though the general disposition of the conducting tissue has now been well documented in most anomalies by morphological studies, the precise location of the atrioventricular bundle and its relation to the crest of septal structures cannot be predicted accurately in each individual case. For such precise localisation intracardiac intraoperative identification of specialis trioventricular conducting tissue by means of a nd eld probe should allow the surgeon to e atrioventricular bundle and its branches. nes permitting such identification have been in various forms over the past decade, mand the assistance of a second observer, way detract to some extent from their is presentation we report on the design, and use of an intracardiac atrio- nduction monitor which does not require a second observer and which incorporates several other advantageous mechanisms.

Desirable design features

It is well established that the atrioventricular conduction system can be identified by detecting the cardiac electrogram produced as the front of depolarisation moves through the system from the atria to the ventricles (Kaiser *et al.*, 1970).

In considering the design of a machine to monitor this activity, it is first necessary to ensure a constantly conducted supraventricular rhythm. To this end the machine was made to provide atrial pacing during intracardiac mapping (Kaiser *et al.*, 1970). A problem encountered during display of the monitored cardiac electrogram is that the normal trace speed used is 25 mm/s. At this speed it is difficult to study the temporal relation of the cardiac electrogram to the electrocardiogram, the PR interval of each complex being represented by only 6 mm of screen width. However, at a trace speed of 650 mm/s the screen width for the PR interval is lengthened to 160 mm, and this was the speed

blication 5 April 1979

chosen for our machine. A major problem with most commercially available detectors is that the surgeon, when manipulating the hand-held probe, unless helped by a second observer, is continually required to alter his field of vision from the heart to an oscilloscope screen. We therefore considered it obligatory to provide an audible signal showing the presence of conducting tissue (Siegel *et al.*, 1974). Finally, we also considered that the hand-held probe should be malleable and should possess a small tip so as to cover as small an area as possible for accurate identification of the specialised tissue.

The machinery to be described was developed in the Medical Electronics Department, Brompton Hospital, and the costing for materials was £980.

Electrode probe

The electrode probe (Fig. 1, 2) is constructed from a stainless steel upper handle and a lower malleable section made of PVC. The tip is made of perspex and on to this are set four silver electrodes 0·5 mm in diameter. A tripolar electrode arrangement has been chosen to eliminate the problem of misorientation. The three measuring electrodes are arranged in the form of an equilateral triangle with a space of 1 mm between each. With this arrangement a cardiac electrogram will always be detected on at least two pairs of electrodes if the probe overlies conducting tissue. A fourth electrode incorporated in the probe tip is used as a reference for the input amplifiers, reducing artefact and interference.

Electronics unit

The electronics unit (Fig. 3, 4) consists of 5 main sections: (1) the oscilloscope; (2) the pacemaker module; (3) the cardiac electrogram module; (4) the electrocardiogram module; and (5) the timing module.

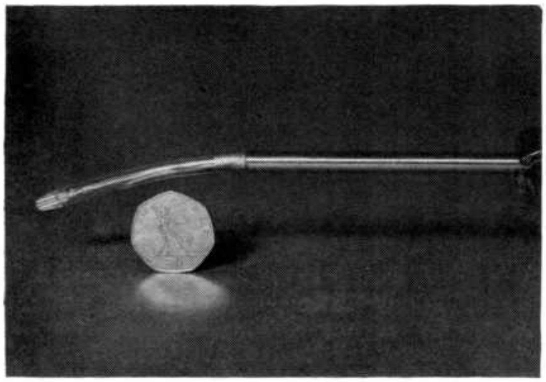


Fig. 1 *Malleable tip intracardiac probe dimensions: 17·5 cm; length of malleable probe: 7 cm.*

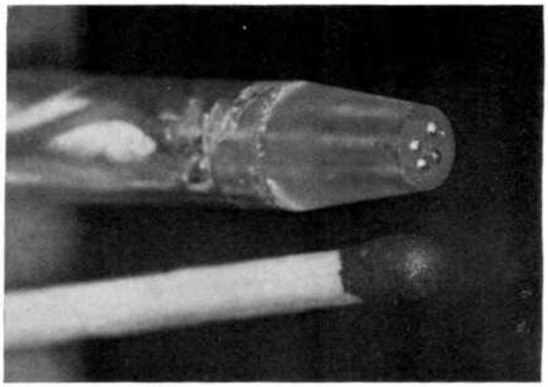


Fig. 2 *Tip of probe. Note quadripolar electrode configurations. Fourth probe is for reference. The three cardiac electrogram probes are in an equalateral triangle 2 mm apart.*

(1) OSCILLOSCOPE

The oscilloscope is of the long persistence type and it has two operating modes. A slow, non-synchronised mode sweeps at 25 mm/s for display of the electrocardiogram before mapping, while a fast 650 mm/s sweep, pacemaker synchronised, is used for mapping. In the latter mode the oscilloscope displays information occurring in the 250 milliseconds post-pacing pulse.

There are 3 traces. The upper trace is used for display of a surface electrocardiogram. The middle trace is in the form of a broken bar of variable width (timing module), the use of which will be explained below, and the lower trace displays the cardiac electrogram signal.

(2) PACEMAKER MODULE

A constant voltage pacemaker with an output pulse width of 2 milliseconds and an amplitude adjustable from 1 to 9 volts is incorporated in the unit. The rate is continuously variable from 60 to 300 beats per minute. Output is available from a socket on the front panel. The output circuit is electrically isolated to provide patient safety. T help identify capture by pacing, a small red lig on the front panel flashes with each pacing pul coincidental with an audible click. By observati it can be noted whether the heart is contracti synchronously with the click. Electrical signals also sent to the oscilloscope to trigger each sw Activation of the pacemaker automatically swi on the oscilloscope in a fast synchronised m 650 mm/s.

(3) CARDIAC ELECTROGRAM MODULE

The cardiac electrogram signals from the electrode probe are fed to an amplifier via a socket on the front panel. The module contains three separate amplifiers, one for each electrode pair, and the amplifiers employ optical isolation for patient safety. Signals are fed to an absolute circuit which converts negative signals to positive and the outputs from the three circuits are then summed to provide a combined signal. This overcomes the situation where the signals from the three input amplifiers might sum to zero. The amplifiers have a frequency response of 40 to 500 Hz and the gain is adjustable with a control on the front panel over a ratio of 10:1. At a minimum gain a 1 millivolt signal across any electrode pair will result in a 1 cm deflection on the screen. A small light at the top of the module glows if the amplitude of the signal is sufficient to result in a deflection of 1 cm on the screen, and the same pulse that activates the light is also fed to the timing module to sound an audio-tone giving the operator evidence of the presence of specialised conducting tissue.

(4) ELECTROCARDIOGRAM MODULE

The module receives a high level electrocardiographic signal from a cardioscope or theatre monitoring equipment. This alleviates the need for an additional set of patient leads. The gain can be adjusted by means of a front panel control and a small lamp on the front will flash with each R wave. A rate meter is incorporated in this module which is digitally displayed and is useful for determining the rate at which to start atrial pacing. The output from this module is fed to the top trace on the oscilloscope and R wave pulse is fed to the timing module.

(5) TIMING MODULE

This generates a timing period or window between the pacing pulse and the R wave which can be adjusted in length, both from its start position, that is time from pacing pulse, and its duration. If a cardiac electrogram pulse is received in the window space an audible tone sounds. This facility allows the operator to set the specific period in which the equipment will indicate the presence of a cardiac electrogram signal and does not indicate artefacts detected outside the time window width.

This module also processes pulses fed from the pacemaker and electrocardiogram module as a check for conducted rhythm. If the pacing capture is lost or heart block occurs it will be detected and indicated by an arrhythmia light on the front panel. When this light is on the audible indication of the cardiac electrogram is muted. The arrhythmia light will become extinguished after five beats when error ceases to exist.

All these modules are housed in one cabinet, 50 × 31 × 24 cm (Fig. 3 and 4). Outputs are provided for the recordings of all signals on to a tape recorder or photographic paper for later study.

Preparation of heart for mapping

Intraoperative identification of the atrioventricular conducting tissues in the open heart when on cardiopulmonary bypass must inevitably have potential risk of air embolism, because it is necessary to allow the heart to beat with the atrioventricular chambers open to the air. It is desirable to monitor the conducting tissue at normothermia. Therefore, after extracorporeal circulation has been instituted by means of ascending aortic cannulation and superior and inferior caval cannulae, on establishing full cardiopulmonary bypass the cavae are snared and the aorta is cross-clamped. A perfusion cannula fed from the side arm of the main aortic perfusion line is then inserted into the aortic root. This allows the aortic root to be perfused, maintains

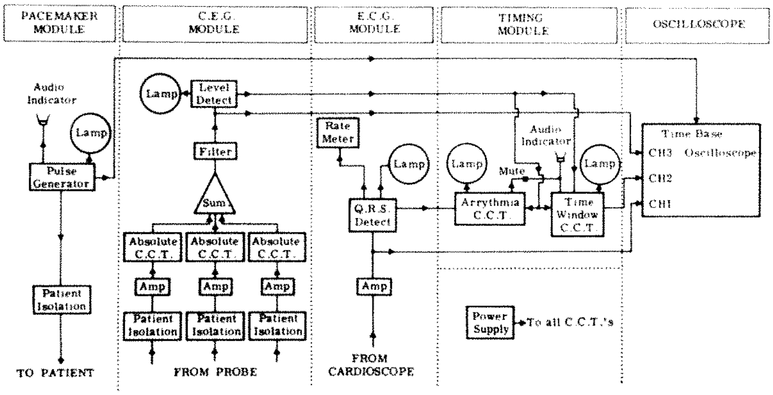


Fig. 3 *Circuit diagram for cardiac conduction monitor. CCT, circuit; Amp, amplifier; CH, channel.*

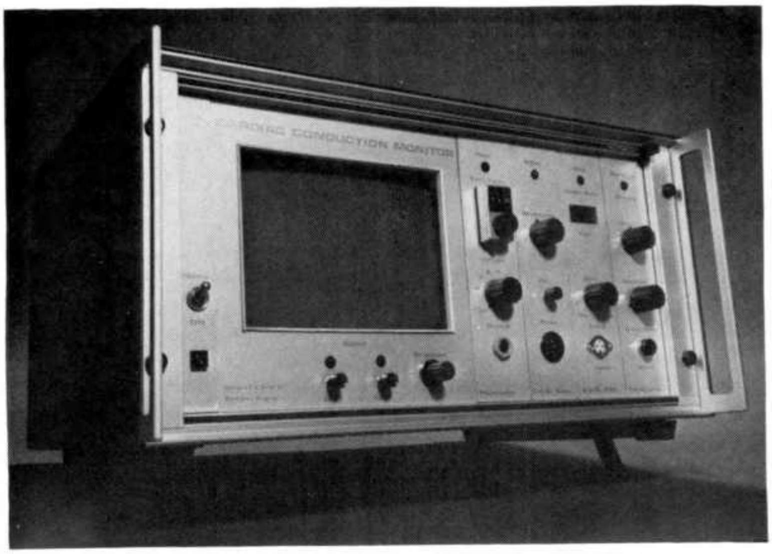


Fig. 4 *The cardiac conduction monitor, together with oscilloscope, housed in a single cabinet with all switches and calibration knobs on the front panel. Dimensions of cabinet: 50 × 31 × 24 cm.*

competence of the aortic valve, and allows coronary perfusion. The heart will then contract normally, even when the cardiac chambers are open.

Artificial pacing of the heart facilitates mapping, thus a pair of pacing electrodes are attached 4 mm apart to the right atrial appendage. This configuration of electrodes has been found preferable to attaching a single active electrode to the atrium and the indifferent electrode to the body tissues.

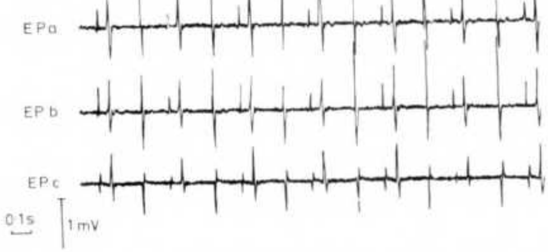


Fig. 5 *Trace from ultraviolet write-out. The surface electrocardiogram (ECG) showing pacing spike and r wave. A cardiac electrogram (CEG) is a summation of electrode probe a, b, and c. The His spike is well seen on the CEG trace. Callibration 0·1 seconds and 1 millivolt.*

Operation

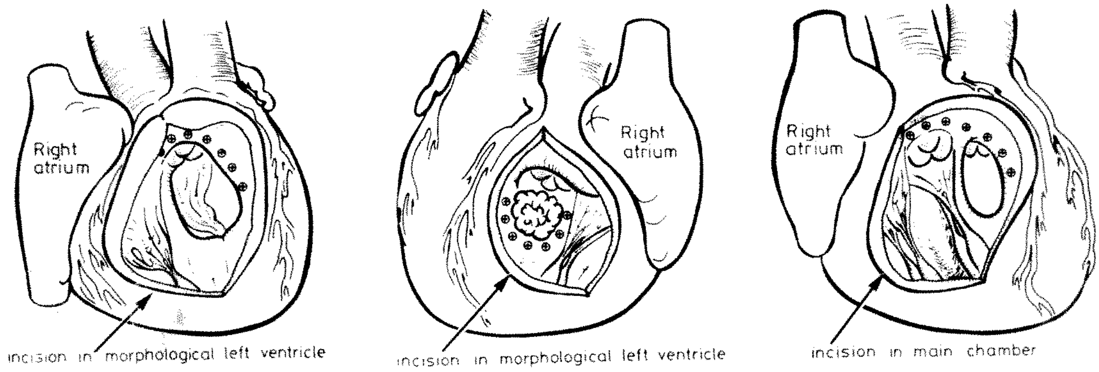
The surface electrocardiogram is connected from a cardioscope to the electrocardiogram module. The heart rate is noted, atrial pacing wires are attached to the patient, and the pacemaker is set to a rate of 10 beats per minute greater than its intrinsic rate. The pacemaker is switched on and capture is achieved by adjusting the rate and voltage controls, at which point the arrhythmia light will extinguish. The oscilloscope will now display the PR interval and the sweep will be 650 mm/s. The time window is set to the required position, the electrode probe is connected, and by manipulating the electrode probe over the surface of the endocardium the operator can conduct intracardiac mapping (Fig. 5).

Examples of use

Over the past year the monitor has b[illegible]d in 29 patients with congenital heart disease [illegible] 2). In 3 with complex congenital [illegible] accurate identification of the non-branch[illegible] proved an invaluable aid to corrective [illegible]

Table 1 *Identification of atrioventricular specialised conducting tissue: on atrial aspect of annulus*

Type of congenital heart disease	*No.*	*Positive*	*Negative*
Atrial septal defect (secundum)	4	4	0
Partial atrioventricular canal defect	6	5	1
Complete atrioventricular canal defect	3	3	0
Tetralogy of Fallot	6	5	1
Ventricular septal defect	7	[illegible]	2
Total	26	22	4


Right atrium
incision in morphological left ventricle
Right atrium
incision in morphological left ventricle
Right atrium
incision in main chamber

a) congenitally corrected transposition in situs solitus

b) congenitally corrected transposition in situs inversus

c) univentricular heart (LV type) with double inlet, left-sided rudimentary chamber

Fig. 6 *Identification of non-branching bundle in (a) congenitally corrected transposition; (b) congenitally corrected transposition with situs inversus; and (c) univentricular heart of left ventricular type with double inlet and left-sided rudimentary chamber. Conductive tissue positive—⊕.*

which was performed without damage to the specialised conducting tissues. These were (i) congenitally corrected transposition (Fig. 6a), (ii) congenitally corrected transposition with situs inversus (Fig. 6b), and (iii) univentricular heart of left ventricular type with double inlet and a left-sided rudimentary chamber (Fig. 6c).

Table 2 *Identification of atrioventricular specialised conducting tissue: on ventricular aspect of annulus*

Type of congenital heart disease	*No.*	*Non-branching bundle*	*LBB*	*RBB*	*Negative*
Ventricular septal defect	7		1	5	1
Tetralogy of Fallot	6		2	4	0
Congenitally corrected transposition in situs solitus	1	1			
Congenitally corrected [illegible] situs [illegible]	1	1			
[illegible] heart with double [illegible] and left-sided rudimentary chamber	1	1			

LBB, left bundle-branch; RBB, right bundle-branch.

Discussion

The pioneering work of Stuckey *et al.* (1960), Kaiser *et al.* (1970), and Siegel and his colleagues (1974) has been drawn upon considerably during the design and preparation of this apparatus. We believe that the completed unit has many advantages over other available designs and machines.

A bipolar electrode system could result in no detection of a cardiac electrogram even when the probe is situated over the conducting tissue, for it is possible for the probe to be so orientated with respect to the advancing front of the depolarisation that a zero potential difference could be present across the electrodes (Siegel *et al.*, 1974; Schatz *et al.*, 1978).

The unit employs electronic circuits to take the absolute value of the signals from each electrode, and then perform a summation. When using this method the possibility of signal cancellation is avoided. The time window configuration displayed on the oscilloscope is similar to that of Siegel *et al.* (1974) and other workers. However, mere use of the time window does not prevent false positive indication occurring in the event of the development of an arrhythmia. In our experience, arrhythmias frequently develop during mapping because of a loss of pacemaker capture, and, as have others, we have noted that the pressure of the electrode probe on the conducting tissue can itself cause temporary atrioventricular dissociation (Schatz *et al.*, 1978). Because of this, we have incorporated circuits into our unit which continuously monitor the pacemaker pulse and the 'R' wave of the electrocardiogram. If an 'R' wave is not detected within a preset time, an arrhythmia lamp is illuminated and the audible bleep, which hitherto had indicated the presence of conducting tissue, is inhibited, thus preventing the recording of false positive signals.

We believe the major advantage of this unit is its simplicity of use for the operating surgeon. It combines, in one instrument, various facilities which in other instruments are separated, in particular, the built-in display oscilloscope with the pacemaker-synchronised time base and the pacing arrhythmia detection circuit. The unit is self contained and requires no additional equipment, facilitating its use at short notice.

It has now been used in 29 patients, being manipulated by the surgeon alone, and has provided identification of the precise localisation of the atrioventricular conduction tissues, whatever the complexity of the malformation (Fig. 6).

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Pericardial tamponade in systemic sclerosis (scleroderma)[1, 2]

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SUMMARY The frequency of pericardial disease in scleroderma found at necropsy is high. The clinical recognition of pericarditis with or without effusion is rare and tamponade with haemodynamic impairment is exceptional.

Three patients with scleroderma presented with an acute syndrome of dyspnoea, chest pain, and cardiomegaly requiring pericardiocentesis for relief of pericardial tamponade. One patient died. The mechanism of the pericardial effusion remains unknown. The haemodynamic data recorded from one patient suggested that pericardial fibrosis in scleroderma may predispose to pericardial tamponade.

Systemic sclerosis (scleroderma) is a multisystem connective tissue disease affecting the heart in several ways. Though myocardial fibrosis and heart block have been considered the most frequent forms of cardiac involvement (Bulkey *et al.*, 1976), in recent years predominant pericardial disease has been documented pathologically (McWhorter and Leroy, 1974). Necropsy studies have noted a 52 to 73 per cent frequency of pericardial disease in scleroderma (McWhorter and Leroy, 1974). The clinical recognition of pericarditis or pericardial effusion is rare and pericardial tamponade with haemodynamic impairment requiring aspiration for relief has not been documented (McWhorter and Leroy, 1974).

We report 3 patients with scleroderma who required pericardiocentesis to relieve hypotension secondary to tamponade. All presented with a similar clinical picture of severe dyspnoea, pleuritic pain, and cardiomegaly (Table 1).

Case reports

CASE 1

An 18-year-old girl presented with a 5-day history of progressive dyspnoea, syncope, and praecordial non-pleuritic pain. She denied fever, chills, cough, or orthopnoea. Scleroderma was diagnosed 3 years previously because of diffuse skin changes, sclerodactyly, Raynaud's phenomenon, proximal myositis, oesophageal aperistalsis, and pulmonary fibrosis.

Physical examination disclosed a temperature of 36°C, heart rate of 120 beats a minute, and a respiratory rate of 36 a minute. Conspicuous diffuse scleroderma skin changes made venous pulsations and accurate blood pressure measurements impossible. Bi-basilar râles and dullness to percussion were present. The heart sounds were distant, but there were no murmurs or added sounds. There was no peripheral oedema.

Routine laboratory studies were normal except

Table 1 *Clinical and laboratory summary*

	Case 1	*Case 2*	*Case 3*
Dyspnoea	+	+	+
Chest pain	+	+	+
Friction rub	0	+	+
Fever	0	+	+
Jugular venous pressure	?	+	+
Hypotension	+	+	+
Tachycardia	+	+	+
Pulsus paradoxus	?	+	+
Kussmaul's sign	?	+	+
Pulsus alternans	?	0	+
Electrocardiogram			
Low voltage	+	+	+
T wave abnormality	+	+	+
Electrical alternans	0	0	+
Chest *x*-ray film			
Cardiomegaly	+	+	+
Pleural effusion	+	+	+
Leucocytosis (10 000/mm³)	+	+	+
Sedimentation rate	ND	+	+

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[2] The opinions or assertions contained here are the private views of the authors and are not to be construed as reflecting the views of the Department of the Air Force or the Department of Defense.

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the white blood cell count (WBC) which was 16 400 mm³, with 68 per cent neutrophils, 29 per cent lymphocytes, and 3 per cent monocytes. Rheumatoid factor was positive, at a titre of 1:32, and antinuclear antibody was negative. Erythrocyte sedimentation rate (ESR) was 15 mm/h. Electrocardiogram showed sinus tachycardia, non-specific ST-T wave abnormalities, low voltage, and incomplete right bundle-branch block. Chest *x*-ray film showed a large globular heart with small bilateral pleural effusions, much changed from a normal film taken 6 months earlier.

The patient's condition worsened within minutes of admission and she suffered a cardiopulmonary arrest. Initial resuscitation was successful and an echocardiogram at that time showed a large pericardial effusion and paradoxical interventricular septal motion. Pericardiocentesis yielded 500 ml serosanguinous fluid and improved her condition but she deteriorated and within several hours died while she was being prepared for a pericardiectomy.

Necropsy showed that the pericardium was thickened with areas of fibrosis and minimal nuclear cell infiltration. Sections of the heart showed no areas of fibrosis and the coronary arteries were normal.

Comment: Primary pericardial disease was present, without congestive heart failure as judged by normal myocardium and the lack of significant pulmonary vascular changes at necropsy.

CASE 2

A 40-year-old white man presented with a 4-day history of left-sided pleuritic pain, fever, and increasing dyspnoea. He had a one-year history of scleroderma with diffuse skin involvement, Raynaud's phenomenon, and oesophageal aperistalsis.

Physical examination disclosed a temperature of 38°C, heart rate 96 beats a minute, respiratory rate 20 a minute, and blood pressure 124/74 mmHg, with an 8 mmHg paradoxical pulse. The jugular veins were distended, but Kussmaul's sign was absent. The lungs were clear, peripheral pulses weak, heart sounds distant, and a pericardial friction rub was present.

Routine laboratory studies were normal except for the WBC which was 16 400/mm³ with 72 per cent neutrophils, 20 per cent lymphocytes, 5 per cent monocytes, and 3 per cent eosinophils. ESR was 43 mm/h. Antinuclear test was antibody positive (1:80) and the latex test was negative. Serum complement, C3 (normal 100 to 200 mg/100 mg), was 35 mg/100 ml.

An electrocardiogram showed low voltage and non-specific ST abnormalities. The chest *x*-ray film showed moderate cardiomegaly and large bilateral pleural effusions. A simultaneous liver-lung scan was consistent with a large pericardial effusion.

On the second hospital day the pleuritic pain increased and a right heart catheterisation showed a raised central venous pressure of 10 mmHg and a pulmonary capillary wedge pressure of 14 mmHg. Prednisone, 100 mg/day, was administered, but the fraction rub became louder and the chest pain increased after 48 hours. The right atrial pressure rose to 30 mmHg, the blood pressure fell to 50 mmHg, and the paradoxical pulse rose [illegible] 30 mmHg. His dyspnoea was quite obvious until emergency pericardiocentesis yielded 350 ml serosanguinous fluid and brought immediate clinical improvement. The haemodynamic changes returned to normal.

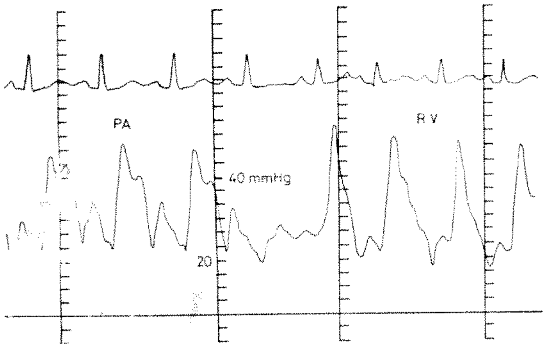
CASE 3

A 48-year-old woman presented with [illegible] history of fever, chills, and pleuritic pa[illegible] obvious dyspnoea on exertion. She had a [illegible] history of scleroderma with Raynaud's phenomenon, sclerodactyly, diffuse skin changes, and oesophageal aperistalsis.

Physical examination disclosed an a[illegible] woman with a temperature of 38·5°C, a heart [illegible] of 100 beats a minute, respiratory rate of 18 a minute, and a blood pressure of 100/60 mmHg, with a 24 mmHg paradoxical pulse and pulsus alternans. Neck veins were distended and Kussmaul's sign was present. Both lung bases were dull to percussion with decreased breath sounds. A pericardial friction rub was present.

Routine laboratory studies were normal except for the WBC which was 13 800/mm³, with [illegible] per cent neutrophils. Antinuclear antibody was positive (1:80). Latex fixation negative and serum C3 [illegible] normal. Electrocardiogram showed a low voltage and electrical alternans. The chest *x*-ray film showed a mildly enlarged globular heart and bilateral pleural effusions. An echocardiogram showed a large anterior and posterior echo-free space and inspiratory increase in right ventricular internal diameter with paradoxical septal motion.

The patient became restless, pale, [illegible] cold within 2 hours of admission when [illegible] blood pressure fell to 86/50 mmHg and no pulse could be felt. Emergency right heart catheterisation showed a mean right atrial pressure of 21 mmHg, right ventricular end-diastolic pressure 20 mmHg, pulmonary artery diastolic pressure 20 mmHg, and a mean pulmonary capillary wedge pressure of 21 mmHg. The pulmonary artery and right ventricular pressure tracings had the classic dip and plateau pattern of constrictive pericardial disease (Fig.). Pericardiocentesis of 550 ml straw-coloured



ight heart pullback pressures in case 3 with d made. The pulmonary artery diastolic ular diastolic pressures are equal and g). Note the early diastolic dip in the pressure curve typical of constrictive

uid brought bout dramatic clinical improvement and normalisation of intracardiac pressure.

T racteristics of the pericardial fluid are able 2 for cases 2 and 3. The pericardial case 1 was not analysed. All cultures for fast bacilli, fungi, and bacteria were negative. rum and pericardial fluid were negative for LE cells in cases 2 and 3.

Discussion

Pericar sion has been considered of little clinic ortance in scleroderma heart disease, whil ocardial fibrosis and atrial or ventricular c ction disturbances have been felt to be the common and clinically significant manifesta- ns (Bulkey *et al.*, 1976). A necropsy study (Bulkey *al.*, 1976) showed that focal or diffuse fibrous pericarditis was present in 17 of 52 patients but the pericarditis was associated with uraemia in 10 patients, myocardial infarction in 1, and severe myocardial fibrosis in 4; only 1 patient had no myocardial or renal disease. D'Angelo *et al.* (1969) compared 58 patients with scleroderma studied at necropsy with age- and sex-matched controls and found pericardial fibrosis and thickening more common in patients with scleroderma. The frequency of pericardial effusion was the same as in the controls though the effusions were larger in volume than those with scleroderma.

Table 2 *ratory characteristics of pericardial fluids*

	Case 2		*Case 3*	
St	*Serum*	*Pericardial Fluid*	*Serum*	*Pericardial Fluid*
ant m³)	16 400	15 800	13 800	310
Segmented cells (%)	75	92	70	18
Glucose (mmol/l)	6·1	4·2	6·6	6·0
LDH (IU/ml)	210	1150	240	2200
Total protein (g/l)	78	64	72	50
Latex fixation	Negative	Negative	Negative	Negative
Antinuclear antibody	Positive	Positive	Positive	Negative
LE cell test	Negative	Negative	Negative	Negative
Culture	Negative	Negative	Negative	Negative
Viral titres	Negative	Negative	Negative	Negative

The clinical diagnosis of cardiac disease in scleroderma differs from findings in necropsy studies; cardiac scleroderma (both myocardial and pericardial) was noted in 16 per cent of 309 patients with scleroderma (Medsger *et al.*, 1971). McWhorter and Leroy (1974) retrospectively studied the pattern and frequency of clinical pericardial involvement in 210 patients with scleroderma and identified 2 forms of pericardial disease. Eleven patients had chronic pericardial effusion and signs compatible with congestive heart failure in the absence of renal failure. Four patients had acute pericarditis associated with dyspnoea, chest pain, and a pericardial friction rub. Pericardial effusion and signs of pericardial tamponade were absent in the 4 patients with acute pericarditis. Of the 11 patients with chronic effusions, 3 developed pulsus paradoxus, Kussmaul sign, or pulsus alternans compatible with early tamponade, but none required pericardiocentesis. This benign course of pericardial disease contrasts with the clinical syndrome of acute pericarditis in our 3 patients with systemic sclerosis who developed severe tamponade necessitating pericardiocentesis. The pattern of the pressure tracings in our third patient showed the classic 'square root sign' or 'dip and plateau' characteristic of very limited ventricular distensibility more usually associated with constrictive pericarditis rather than tamponade (Shabetai *et al.*, 1970). It is conceivable that with the relative incapacity for distension in scleroderma complicated by pericardial fibrosis only a small volume of pericardial fluid may precipitate pericardial tamponade.

The aetiology of pericardial effusion in scleroderma remains unclear, but was not secondary to renal failure, heart failure, or infection in our patients, nor was there strong evidence to suggest an immunological pathogenesis.

Pericardial disease is the most common form of cardiac involvement in systemic sclerosis (D'Angelo *et al.*, 1969), though Bulkey *et al.* (1976) showed that cardiac dysfunction is usually secondary to myocardial disease. We have shown that pericardial disease may cause acute pericarditis and pericardial tamponade requiring aspiration.

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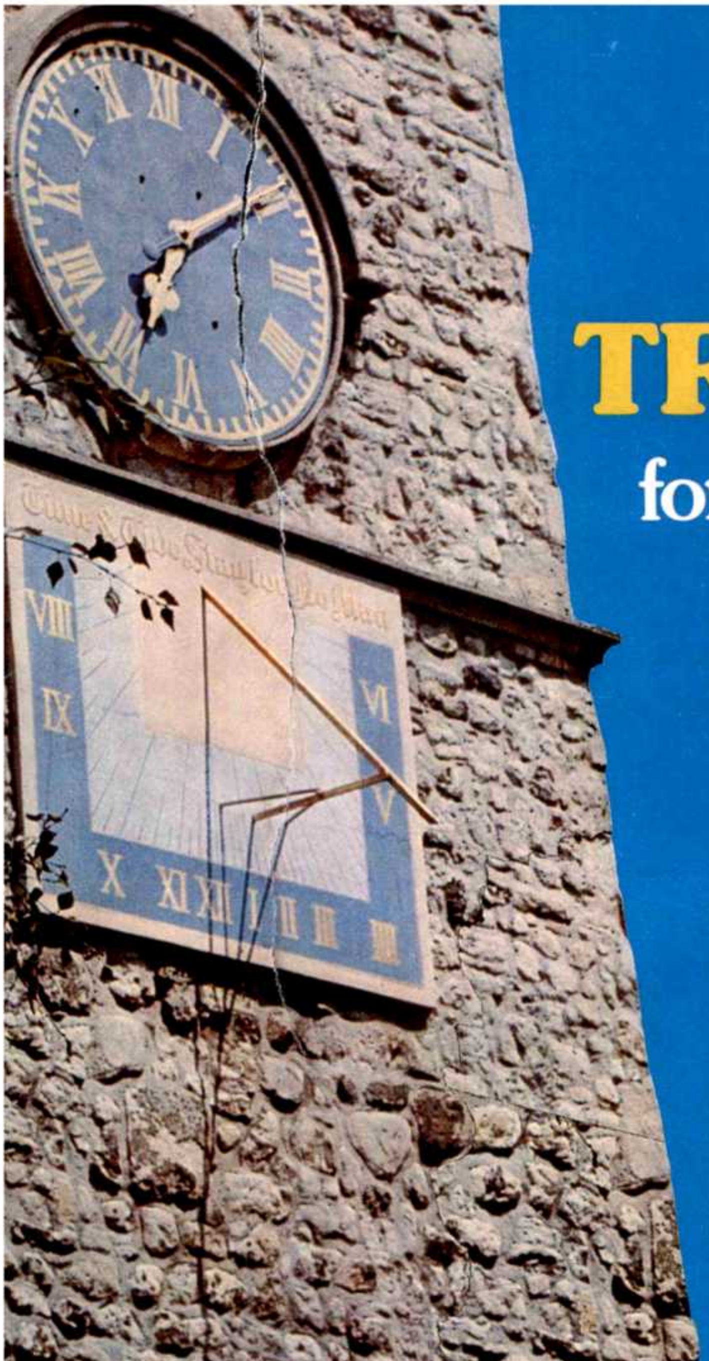

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Case reports

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Infective endocarditis with glomerulonephritis associated with cat chlamydia *(C. psittaci)* infection

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SUMMARY A patient with glomerulonephritis and endocarditis is described who had evidence of feline *Chlamydia psittaci* infection. Treatment with antichlamydial drugs resulted in resolution of the glomerulonephritis and the endocarditis. It is recommended that screening for chlamydia is included in the investigation of patients with suspected or obscure endocarditis.

Infective endocarditis is often caused by an unusual organism. The management of such cases is much more effective if the identity of the organism has been established (Friedberg, 1964; Hampton and Harrison, 1967).

We describe a patient with infective endocarditis and secondary glomerulonephritis in whom there was strong evidence of infection with the feline keratoconjunctivitis agent (*Chlamydia psittaci*). This is the first recorded case of endocarditis and glomerulonephritis caused by this organism.

Case report

A 40-year-old man who worked as a steward on a cross-channel ferry was admitted to hospital in December 1976 for investigation of proteinuria. His past illnesses included gonorrhoea in 1972. In May 1976 he developed a pale red-yellow rash over the limbs and trunk with a purpuric component on the legs. This was accompanied by gingivitis, fever, night sweats, and sore throat. Investigations were done in a hospital in Antwerp and showed: Hb 11 g/dl, white cell count 11·8 × 10^9/l (76% lymphocytes), and ESR 83 mm in the first hour. The monospot and Paul-Bunnell test for infectious mononucleosis were negative. The RA latex test was positive and the Rose-Waaler 1/40. β1A/β1C complement was low. IgM was 5·8 g/l (0·38-1·45), IgG was 22 g/l (6-18), and IgA was normal. The blood urea was 9·5 mmol/l (57 mg/dl) and the serum creatinine 185 μmol/l (2·2 mg/dl). Hepatic enzymes were mildly increased but the serum bilirubin was normal. The urinary protein concentration was 1·6 g/l and the sediment contained numerous red blood cells. Skin biopsy and rectal biopsy showed nonspecific acute vasculitis and liver biopsy a mild nonspecific hepatitis. He was given intramuscular penicillin for 12 days for his gingivitis and also prednisone 20 mg daily for 4 weeks.

In July 1976 in Winchester though generally well, he had lost 2 stones (12·7 kg) in weight. He had the signs of aortic regurgitation not previously recorded but no other evidence of endocarditis. The urine again contained large amounts of protein and blood. Renal function was otherwise normal. Serum complement C3 and C4 were decreased. Chest *x*-ray and electrocardiogram were normal. The patient was anxious to return to sea and did not reattend until December 1976. At that time he had a urethral discharge. Smears were negative for gonorrhoea and serological tests for syphilis were negative.

He agreed to further investigation in hospital because of increasing exertional dyspnoea over 4 weeks. He had also noted intermittent haematuria and mild night sweats since his illness in May 1976. Physical examination again showed only signs of aortic regurgitation, proteinuria, microscopical haematuria, and casts. His temperature was persistently 38 to 39°C. Investigations showed normochromic anaemia—haemoglobin 8·7 g/dl, white cell count 9·0 × 10^9/l, and platelets 267 × 10^9l; ESR was 139 mm in the first hour. The blood urea was 15·0 mmol/l (90 mg/dl) and serum creatinine 175 μmol/l (2·0 mg/dl). The antistreptolysin 0 titre was 200 IU/ml. Salmonella and brucella agglutinins

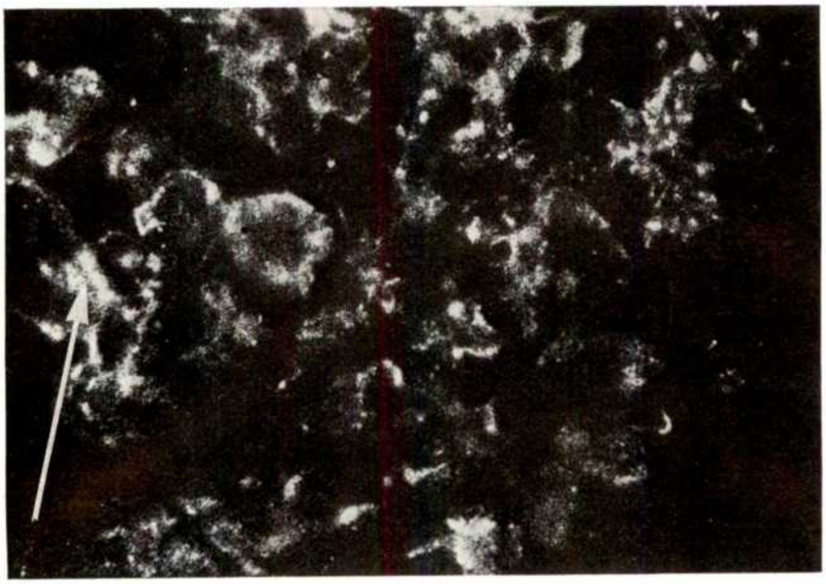

Fig. 1 *Glomerulus containing granules of complement (C3) in the capillary walls and mesangium (arrow). IgM is found in a similar distribution. (FITC-swine-antihuman C3 × 450.)*

and complement fixation tests were negative as was the Q fever complement fixation test and fungal precipitins. Repeated blood cultures were negative. The RA latex test was negative. Plasma contained type M mitochondrial antibody to a titre of 1/40. Serum complement was decreased C3 at 0·35 g/l (1·0-1·8) and C4 at 0·09 g/l (0·14-0·38). Hepatitis B antigen was negative. Immunoglobulins IgG 28·4 g/l (7-13) and IgM 3·1 g/l (0·4-1·3) were again increased and IgA 2·0 g/l (1·2-3·5) was normal. Sternal marrow aspirate was normal. Renal biopsy showed proliferation of mesangial and endothelial cells and immunofluorescent examination revealed numerous fine granules of IgM and C3 in the basement membranes (Fig. 1).

Eight days after admission the patient experienced the sudden onset of weakness of the left side of his face and body. This resolved rapidly over the next 24 hours. It was thought that he had a cerebral embolus from an infected aortic valve and immediate antibiotic therapy was begun with intravenous penicillin and gentamicin. However, 6 days later he had a further severe left hemiparesis with grossly impaired consciousness. As his fever had still not settled several days later and the cause of the presumed endocarditis was not identified, the antibiotics were changed to ampicillin and clindamycin. Ten days later the psittacosis/lymphogranuloma venereum complement fixation test was > 1:256 on plasma taken soon after admission and > 1:256 on 2 further specimens. Type specific antichlamydial antibody testing by the modified micro-immunofluorescent method (Treharne *et al.*, 1977) revealed specific antibody against the cat chlamydial type of *C. psittaci* (cat keratoconjunctivitis agent) in titres of IgM 1/64 and IgG 1/1024. In view of this result and the continued spiking fever antichlamydial treatment was begun with erythromycin (tetracycline being avoided because of the renal failure). The temperature returned to normal within 4 days and remained so. Serial measurements of serum complement and creatinine showed both returning to normal (see Fig. 2). Clinical improvement also occurred with return of full consciousness and reversal of weight loss. Despite improvement in the hemiparesis there was some mild persistent intellectual deficit. The ESR returned to normal and the proteinuria and haematuria completely disappeared. Four months after the antichlamydial treatment was begun, antichlamydial antibody levels as measured by the micro-immunofluorescent test had fallen to 1/256 for IgG and less than 1/8 for IgM. Doxycycline was substituted for erythromycin as soon as the patient could reliably take oral medication and will be continued for one year.

Discussion

Although the aetiological agent of this patient's infective endocarditis was not isolated there is serological evidence that the organism responsible was the feline chlamydial agent (feline keratoconjunctivitis agent), a type of *C. psittaci*. The presence of specific antibody (IgM 1/64 and IgG 1/1024)

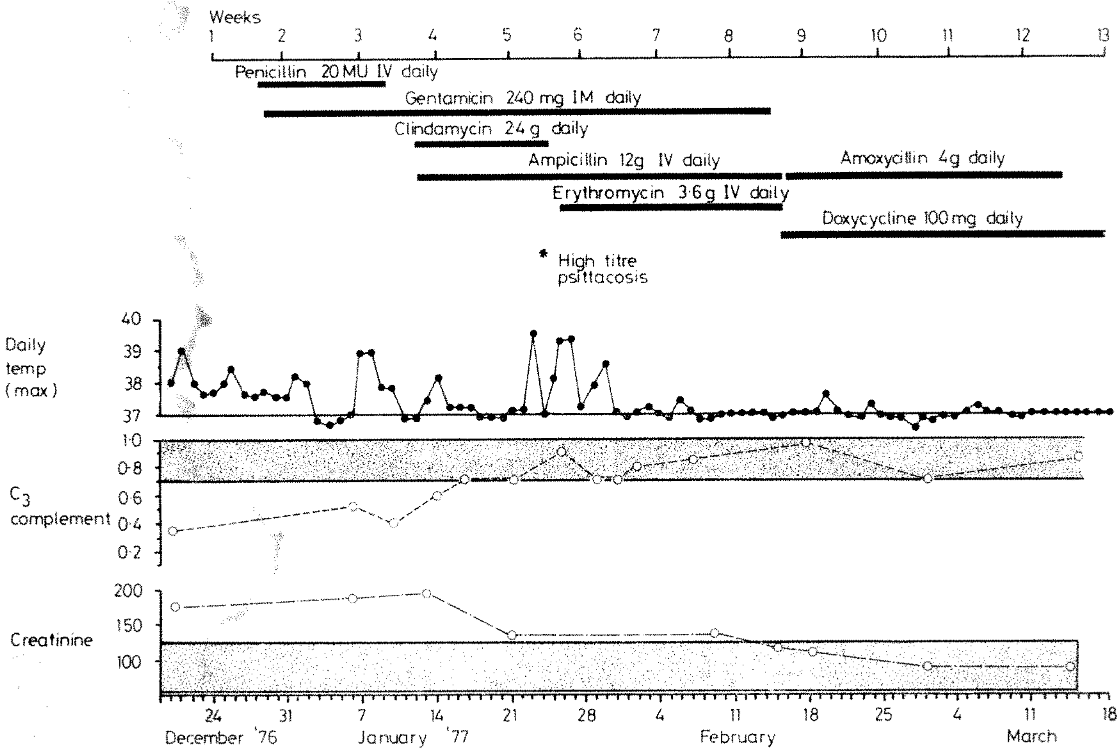

Fig. 2 *Serial readings of the patient's temperature, serum complement, and serum creatinine are plotted against time. Antibiotic therapy is also shown. All indices returned to normal.*

against cat chlamydia in this patient is highly suggestive of an active infection with this agent. The cat chlamydia agent has previously been shown to cause conjunctivitis in man (Ostler *et al.*, 1969). There have been previous reports of infective endocarditis caused by *C. psittaci* (Levison *et al.*, 1971) (none of those with complicating glomerulonephritis have recovered). However, antichlamydial antibody type-specificity was not determined. Levison described 2 cases and cited several previous reports. Most, but not all, of these patients gave a history of contact with birds. In another study (Ward and Ward, 1974) it was suggested that *C. psittaci* might be aetiologically related to some cases of chronic valvular heart disease. Of 7 patients in whom antigen of *C. psittaci* was identified in the endocardium, 2 had no history of contact with birds. It is possible that in some of these patients the cat chlamydial agent could have been present but *C. psittaci* typing was not done.

Our patient gave a history of prolonged close contact with cats. His fever responded to antichlamydial treatment (erythromycin). After antichlamydial treatment, the level of antichlamydial IgG and IgM directed against cat keratoconjuctivitis had fallen fourfold or more (from 1/1024 to 1/256 and 1/64 to less than 1/8, respectively). The earlier response of the low C3 complement may have been the result of a partial antichlamydial effect of clindamycin. His proteinuria and haematuria disappeared and the renal function returned to normal on continued antichlamydial treatment with erythromycin followed by doxycycline alone since March 1977. The progress of his aortic regurgitation was arrested from the time of effective treatment of his endocarditis.

The occurrence of glomerulonephritis in association with infective endocarditis is well recognised (Gutman *et al.*, 1972). This nephritis is probably the result of deposition of immune complexes of which the antigen is derived from the infective organism (Levy and Hong, 1973; Perez *et al.*, 1976). One of the patients with endocarditis caused by psittacosis reported by Levison *et al.* (1971) had glomerulonephritis confirmed at necropsy. Our patient had histologically proven glomerulonephritis of which all clinical evidence disappeared on antichlamydial therapy, presumably because of removal of the antigen. The presence of IgM rather than IgG in the kidney is unusual, but has been noted previously in association with endocarditis (Perez *et al.*, 1976).

This patient appears to be the first in whom the feline keratoconjunctivitis agent type of *C. psittaci* has been implicated in infective endocarditis. He is also the first patient reported whose chlamydial endocarditis was effectively treated with arrest of aortic regurgitation and cure of associated glomerulonephritis.

A history of contact with cats should be sought, along with that of contact with birds, in patients with infective endocarditis where the cause is unclear. A negative history does not exclude the diagnosis. We recommend also that such patients are screened for psittacosis/lymphogranuloma venereum antibody and if positive specific chlamydial typing should be done. Ideally one would like definitive demonstration of the organism. This is unlikely to be achieved at present unless the infected valve should need to be removed.

Thanks are due to Dr A. G. MacIver, University of Southampton, for the histological photographs and to Dr S. Darougar, of the Institute of Ophthalmology, University of London, for advice on the preparation of the discussion.

Addendum

The patient required aortic and mitral valve replacement for deteriorating left ventricular failure in February 1978. The valves showed no evidence of active endocarditis, but microscopically there were a few small vegetations. Cultures, including yolk sac culture, were negative, as was electron microscopy. He recovered well postoperatively, but died in another hospital one month later of an acute respiratory illness. Necropsy showed bilateral bronchopneumonia. The prosthetic heart valves appeared normal.

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Endocarditis caused by *Salmonella enteritidis*

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SUMMARY A case of endocarditis caused by *Salmonella enteritidis* is reported in a 20-year-old African woman. This is only the fourth published case. The development of this rare infection in the patient reported here probably resulted from a reduction in immunity caused by pregnancy and a past splenectomy.

Salmonella enteritidis is a relatively common bowel pathogen, but is an exceedingly rare cause of endocarditis. Only 3 cases have been previously recorded, and only one (an infected prosthesis) was absolutely proven by culture of vegetations. This paper records a further definite case involving infection of a rheumatically damaged mitral valve in an African woman.

Case report

During her first pregnancy a 20-year-old Zambian woman became ill with fever, vomiting, myalgia, and cough. Eight years previously she had undergone splenectomy for an obscure haemolytic anaemia. There were no other details available and she had remained well after operation. Examination disclosed a sick looking girl with a 24-week size uterus. She was moderately anaemic and icteric, and her temperature was 39°C. She also had signs of moderately severe pure mitral regurgitation, with left ventricular hypertrophy. Her liver was enlarged 5 cm but there were no other signs of heart failure. Investigations showed a haemoglobin of 9·4 g/dl, white cell count 37 400 mm^3 (80% neutrophils), and a blood film revealed polychromasia, nucleated red cells, macrycytosis, and Howell-Jolly bodies. Repeated malarial slides were negative as was a Coombs test. Haemoglobin electrophoresis was AA, and glucose-6-phosphate dehydrogenase level was normal. Serum bilirubin was 117 μmol/l (reference range 1·7-17 μmol/l), with 92 μmol/l unconjugated and 25 μmol/l conjugated. Alkaline phosphatase and aspartate transaminase levels were normal. A high vaginal swab and stool culture were sterile, but blood and urine cultures grew *S. enteritidis*.

A diagnosis of rheumatic mitral rregrgitation with acute endocarditis due to *S. enteritidis* was made. Because of the septicaemia and past splenectomy it was felt that no firm evaluation of the haemolytic anaemia could be made. Treatment was begun with parenteral gentamicin 240 mg/day, ampicillin 2 g/day, and chloramphenicol 2 g/day. Digoxin and diuretics were later added when signs of overt heart failure appeared. She slowly improved, and treatment was stopped 4 weeks later, though she still had a mild fever and anaemia. Her recovery was further complicated by premature labour, which was suppressed with sedation, bedrest, and salbutamol. Two months after her original presentation she suddenly deteriorated, developing a high swinging fever, increased anaemia, and severe heart failure. She died 2 days later in refractory heart failure, and 4 blood cultures taken before her death subsequently grew *S. enteritidis*.

At necropsy the mitral valve was found to be fibrosed and regurgitant with extensive vegetations, which grew *S. enteritidis* on culture.

Discussion

Endocarditis caused by *S. enteritidis* was first recorded by Saphra and Winter (1957) in their review of 7779 salmonella infections; but apart from the illness being fatal no other details were given. Yamamoto *et al.* (1974) reported a probable case in a woman with a mitral valve prosthesis, but though blood cultures were positive and the illness typical, the valve did not grow *S. enteritidis* when cultured after surgical removal. Both these reports were from North America, but the third case was from Britain and involved a man with a prosthetic aortic valve in whom *S. enteritidis* was isolated from blood cultures as well as the valve when it was removed *post mortem* (Shanson *et al.*, 1977).

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In the case reported here it was interesting that there was apparently no preceding bowel infection with *S. enteritidis*, which occurred in the reports of Yamamoto *et al.* (1974) and Shanson *et al.* (1977). Presumably the immuno-suppressant effects of pregnancy and splenectomy led to the development of this unusual infection, though the route of entry is obscure. Of the 4 cases now recorded only the patient of Yamamoto *et al.* (1974) survived, emphasising the seriousness of the condition. These workers used valve replacement with high dose parenteral ampicillin before and after operation. Shanson and his colleagues (1977) consider that the addition of mecillinam to this regimen provides the present optimum treatment.

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British Heart Journal, 1979, **42**, 355–358

Isolated congenital absence of coronary sinus

R. A. FOALE, D. W. BARON, AND A. F. RICKARDS

From the National Heart Hospital, Westmoreland Street, London, and Cardiothoracic Institute, Beaumont Street, London

SUMMARY A case is reported in which contrast angiography showed complete absence of the coronary sinus, the cardiac veins draining separately into left and right atria. Normal systemic venous drainage was demonstrated by contrast cross-sectional echocardiographic methods and later confirmed by conventional angiographic injections. In addition, angiography showed a stenosis in the anomalous cardiac vein draining into left atrium accounting for the presence of a continuous murmur for which the patient was initially referred.

Absence of the coronary sinus is a rare congenital anomaly which has previously been described in association with other cardiovascular abnormalities. In particular, Raghib *et al.* (1965) described a developmental complex consisting of persistent left sided superior vena cava draining into left atrium, an atrial septal defect, and absence of the coronary sinus. Congenital absence of this structure has also been described in association with atrioventricular canal defects and other complex forms of congenital heart disease (Mantini *et al.*, 1966). To our knowledge no case of complete absence of the coronary sinus occurring as an isolated anomaly has been previously reported.

Case report

A 59-year-old woman was referred for evaluation of a cardiac murmur, her only symptom being fatigue. Twelve months previously mild hypertension had been noted and cyclopenthiazide was administered, with satisfactory blood pressure control. There was no past history of rheumatic fever, respiratory disease, or chest trauma. However, a cardiac murmur had been noted during her first pregnancy at the age of 23.

On examination the pulse rate was 80/minute, regular with a normal waveform. Blood pressure was 140/80 mmHg in both arms, supine and standing. The jugular venous pulse was normal. There was no abnormal praecordial impulses or thrills. Auscultation revealed normal heart sounds and at the second left intercostal space a continuous soft high-pitched murmur with late systolic accentuation. The murmur was unaffected by posture, respiration, or occlusion of the neck veins. The remainder of the physical examination was normal.

The resting electrocardiogram showed symmetrical T wave inversion in lead aVL with an upright P wave. The plain chest *x*-ray film was normal. The phonocardiogram using a high frequency filter with the transducer in the second left intercostal space documented the continuous murmur which was unaffected by respiration. Single crystal M-mode echocardiogram was normal. A 12 lead maximal treadmill exercise test was performed using the Bruce *et al.* (1973) procedure, during which an ear lobe oximeter[1] measured peripheral arteriolar oxygen saturation continuously. The patient achieved stage two with a heart rate of 140/minute, the test being limited by tiredness. A distinct increase in the intensity of the murmur was observed immediately after exercise. Oximetry revealed a gradual fall in oxygen saturation from a resting desaturated level of 93 to 86 per cent two minutes after exercise (Table). The phonocardiogram was repeated with ear lobe oximetry measurements after sublingual administration of 1·0 mg glyceryl trinitrate. The intensity of the murmur gradually increased to a peak at three minutes (in agreement with the auscultatory findings), there being no change in peripheral oxygen saturation.

In order to exclude arteriovenous fistula cardiac catheterisation with coronary arteriography was performed (Sones technique). No left-to-right shunt was detected on oxygen saturations and the atrial septum appeared intact. There was mild arterial desaturation at rest of 93 per cent, in agreement with the ear lobe oximetry measurements. Left ventriculography and coronary arteriography were normal. After the left coronary artery injection,

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[1] Hewlett-Packard 47201A.

Table *Oximetry measurements during treadmill test*

Stage (Bruce)	*Heart rate*	*12 lead electrocardiogram*	*Blood pressure (mmHg)*	*Arteriolar SO_2*
Rest	88	N	130/80	93%
Stage 1	134	N	160/85	—
Stage 2	142	N	170/90	—
Immediate PE	138	N	165/85	88%
2 minute PE	118	N	140/80	86%
4 minute PE	106	N	135/80	91%
6 minute PE	104	N	130/70	94%

Decrease in arteriolar ear-lobe oxygen saturation caused by increased right-to-left shunting (coronary venous efflux to left atrium) after exercise.
PE, postexercise; N, normal.

however, follow-through to the venous phase failed to opacify the coronary sinus, the left venous system draining into the great cardiac vein which had a fixed stenosis near its origin (Fig. 1a). This vein then drained into a normal sized left atrium. Right coronary arteriography in the venous phase opacified the posterior interventricular vein draining into a normal right atrium (Fig. 1b). Between these veins draining separately into left and right atrium no coronary sinus was seen.

Cross-sectional echocardiography was performed using an 81° mechanical sector scanner[1] and three bolus injections of indocyanine green (Sahn *et al.*, 1974) given separately via left and right antecubital veins and right femoral vein. Systemic venous return was shown to be normal by the rapid appearance of 'contrast echoes' within the right

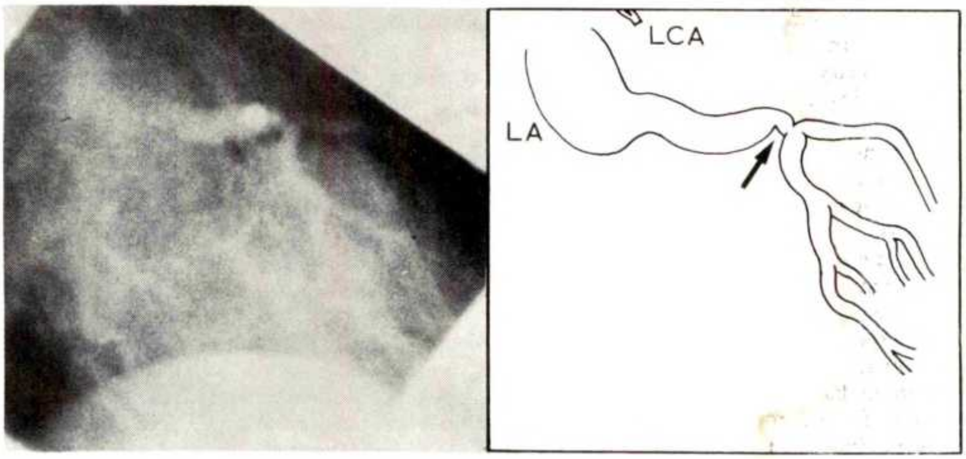

Fig. 1 (a)

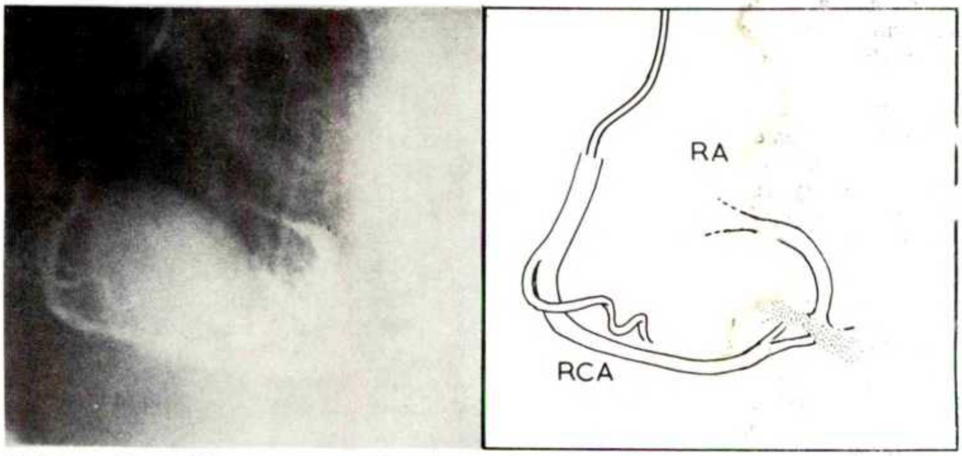

Fig. 1 (b)

Fig. 1 (a) *Venous phase of left coronary artery injection demonstrating stenosis at origin of great cardiac vein (arrow), filling of left atrium (LA), and catheter tip in left coronary artery (LCA). The coronary sinus is absent in the posterior left atrioventricular groove.* (b) *Right coronary artery (RCA) injection with venous efflux into the right atrium (RA).*

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[1] Smith Kline Instrument Corporation.

atrium only (Foale *et al.*, 1979). This was subsequently confirmed by conventional injections of radio-opaque contrast medium.

The patient's symptoms remain stable and have required no treatment.

Discussion

Although coronary venous drainage is usually fairly constant, several anomalies have been described (Mantini *et al.*, 1966; Helseth *et al.*, 1974). Absence of the coronary sinus is rare and is usually associated with other abnormalities, the commonest being an atrial septal defect with persistent left sided superior vena cava terminating in left atrium.

The coronary sinus is the major channel of cardiac venous return and 96 per cent of all veins which drain left ventricular myocardium (including the interventricular septum) efflux into this structure (Hood, 1968). In the posterior atrioventricular groove the coronary sinus receives the great cardiac vein which drains the anterolateral aspect of the heart via anterior interventricular and left marginal (diagonal) veins. The coronary sinus is formed laterally in the atrioventricular groove by the junction of the great cardiac vein with the oblique vein of the left atrium (vein of Marshall), the embryonic remnant of the left superior cardinal vein. This junction is often marked by an indentation produced by the venous valve of Vieussens. The coronary sinus transports 85 per cent of total coronary blood flow (Gensini *et al.*, 1965) and normally terminates on the inferomedial wall of the right atrium.

Anomalies of the coronary sinus are usually described as benign conditions or as part of more complex congenital cardiac malformations. Enlargement with persistence of a left sided superior vena cava is the most frequent anomaly, occurring in between [illegible]5 and 4 per cent of patients with congenital heart disease (Campbell and Deucher, 1954). Rarely, enlargement of the coronary sinus may be the result of communication between left atrium and coronary sinus ('unroofed coronary sinus'), with a resulting low pressure left-to-right shunt, or between coronary artery and coronary sinus (coronary artery fistula) resulting in a high pressure shunt. Very rarely, the ostium of the coronary sinus may be atretic, with the sinus ending in a blind sac. Drainage back to the right atrium is usually via an associated left sided superior vena cava, left innominate vein, and right superior vena cava. Complete absence of the coronary sinus has not hitherto been described as an isolated anomaly. When previously reported it has been in association with other anomalies, most commonly persistent left sided superior vena cava terminating in left atrium with an atrial septal defect (located posteroinferiorly to the fossa ovalis). In these cases the cardiac veins drain separately into their corresponding atria (Raghib *et al.*, 1965).

In the case reported, no coronary sinus was seen during the venous phase of either coronary artery injection, left and right venous channels draining into their respective atria. The stenosis present in the venous channel draining into left atrium was best seen in the left anterior oblique projection, and corresponded to the site of the valve of Vieussens, where the oblique vein of Marshall joins the great cardiac vein to form the coronary sinus. We propose that this venous stenosis (in a major vein draining left ventricular efflux) was the cause of the continuous murmur in the patient. The distinct increase in intensity of the murmur after exercise and glyceryl trinitrate was, we believe, caused by increased venous return across the stenosis consequent upon an increase in myocardial blood flow. The further decrease in systemic oxygen saturation on exercise reflects both increased myocardial oxygen extraction and increased myocardial blood flow with an increase in right-to-left shunting. After administration of glyceryl trinitrate, however, systemic arterial desaturation remained the same, probably because increased myocardial blood flow was accompanied by a concomitant decrease in myocardial oxygen extraction.

This case also demonstrates the application of contrast cross-sectional echocardiography in patients suspected of having anomalous systemic venous return. It is unique in that congenital absence of the coronary sinus is described as the sole cardiac abnormality.

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oprolol and propranolol

British Heart Journal, 1979, **42**, 359–361

Noradrenaline producing phaeochromocytomas with ab n pressor response to beta-blockade

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Médicale Propédeutique, Hôpital Broussais, 96 rue Didot, 75014 Paris, France

patients with phaeochromocytoma, effective beta-blockade was obtained with pro-
twice a day for 3 days) or acebutolol (400 mg twice a day for 3 days) without any effect
sure. In both patients the excretion of noradrenaline predominated over that of adrena-
found in most cases of phaeochromocytoma. A hypertensive response to beta-blockade
expected in patients with an adrenaline-secreting tumour. It cannot be a regular event or
gnostic test in patients with suspected phaeochromocytoma.

blockade can unmask the alpha-
tor action of adrenaline in man
1977). A hypertensive effect of
been described in phaeochromo-
ard and Ross, 1966). Yet neither
propranolol had any effect on the
2 of our patients with phaeo-

consecutive patients with phaeo-
9 had been given beta-blockers
mocytoma was diagnosed (pro-
tolol in 2, and oxprenolol in 1).
tients reported an increase in
to hypertension, and no evi-
blood pressure was reported in
rate data were available in the

was referred on account of a
190/124 mmHg. She had had
headache for 13 years. Anti-
stopped a month before
r complete investigation.
screening for catecholamines
with acebutolol in which
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after 3 days on placebo and
00 mg twice a day (Ménard
kade by acebutolol decreased
er cent and the plasma renin
ent but had no effect on the
g). Phaeochromocytoma was
hour urinary excretion of vanillylmandelic acid (46 mmol), metanephrinee (2395 mg), noradrenaline (6413 nmol), and adrenalins (224 nmol). Angiography showed a mass in the right adrenal. A phaeochromocytoma weighing 25 g was removed and thereafter the patient was normotensive.

A 49-year-old man was referred because of high blood pressure, 210/132 mmHg. His hypertension was asymptomatic and untreated. Investigations included a therapeutic test with propranolol 40 mg twice a day conducted as described above for acebutolol. After 3 days on propranolol, the heart rate decreased by 20 per cent, and plasma renin activity by 90 per cent, but the blood pressure was unchanged (Fig.). The 24-hour urinary excretion of vanillylmandelic acid, metanephrines, nonadrenaline, and adrenaline was 46 mmol, 1190 mg, 728 nmol, and 6 nmol, respectively. A phaeochromocytoma was removed from the left adrenal and the patient became normotensive.

Discussion

A potential danger of beta-blockade in patients with phaeochromocytoma is the paradoxical rise in blood pressure linked to 'adrenaline reversal': Dornhorst and Laurence (1963) stated that administration of pronethalol 'to patients with phaeochromocytoma not already receiving phenoxybenzamine might cause a serious rise in blood pressure by abolishing the dilator (beta) action of adrenaline on peripheral vessels, especially in muscle, while leaving the constrictor (alpha) actions unopposed'. In 5 patients with phaeochromocytoma, Prichard and Ross (1966) found a

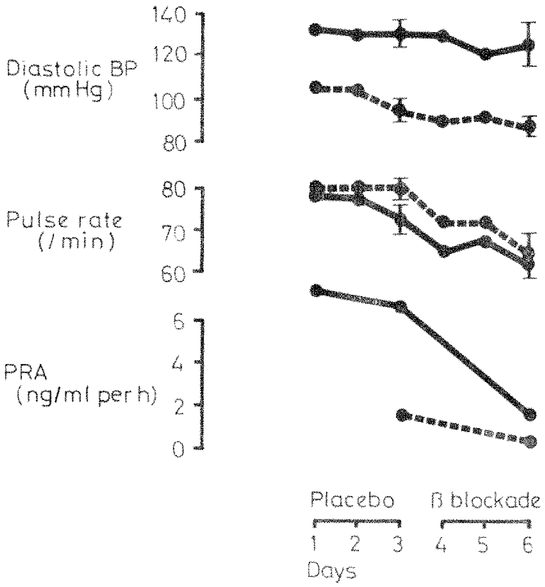

Fig. *Effects of beta-blockade on diastolic blood pressure, pulse rate, and plasma renin activity in 2 patients with phaeochromocytoma.*
The first patient (solid line) received acebutolol 400 mg twice a day; the second patient (broken line) received propranolol 40 mg twice a day. Values for supine diastolic blood pressure (diastolic BP) and pulse rate are the means of 5 determinations (± 1 SD) at day 3 and day 6, and the means of 2 determinations on the other days. PRA, plasma renin activity after walking for 1 hour.

rise in blood pressure after administration of propranolol. The rise in blood pressure was neither dose-related nor constant. In fact, it occurred in only 12 out of 20 experiments with doses ranging from 10 to 100 mg orally. The authors did not state how variability in blood pressure was taken into account in defining the control levels, but they did suggest that the vasopressor response to propranolol may be of diagnostic value in phaeochromocytoma.

Since the report by Prichard and Ross (1966), there has been little recorded evidence to support the assertion that beta-adrenergic blockade may evoke a hypertensive response in phaeochromocytoma. Thomas *et al.* (1977) reported an immediate fall of the blood pressure in a patient with phaeochromocytoma after intravenous practolol. Briggs *et al.* (1978) saw a hypertensive response in a patient with an adrenaline-secreting phaeochromocytoma treated with labetalol. In the 2 cases reported by Wark and Larkins (1978), pulmonary oedema followed several days or weeks after the introduction of propranolol, but in neither patient was the blood pressure raised.

In our patients the effectiveness of beta-blockade was shown by a consistent decrease in heart rate and plasma renin activity. The absence of a fall in blood pressure in response to beta-blockade suggests that the renin-angiotensin system was not contributory in maintaining the hypertension. The absence of a rise in blood pressure is at variance
with the suggestion of Prichard and Ross (196
possible explanation for this discrepancy i
first patient is her having had a beta-1
antagonist, acebutolol, whereas the pa
Prichard and Ross had propranolol: i
volunteers, Johnsson (1975) found the m
pressure was decreased during adrenal
unchanged during infusion of adr
metoprolol (another beta-1 receptor
and increased during infusion of ad
propranolol. A more likely explan
our patients is the dominance of
over adrenaline production, since it
in hypertensive men that beta-blo
modify the pressor response to
(Vlachakis *et al.*, 1977).

Beta-blockers are widely used in
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Correspondence

British Heart Journal, 1979, **42**, 362–363

Diazoxide in treatment of primary pulmonary hypertension

Sir,

After reading the report by Wang *et al.* in the *British Heart Journal* (1978, **40**, 572–574), we attempted a trial of diazoxide in a patient with primary pulmonary hypertension. The outcome suggests caution in the use of this drug in such patients.

A 39-year-old woman with severe pulmonary hypertension with no apparent cause had previously undergone unsuccessful trials of oxygen, nitroprusside, isoprenaline, and tolazoline during cardiac catheterisation. In August 1978 diazoxide was injected into the main pulmonary artery, and haemodynamic measurements were taken 5 minutes after each dose using the procedure described by Wang *et al.* (1978). The results are given in the Table.

Diazoxide	*Heart rate (beats/min)*	*CO (l/min)*	*Pulmonary artery pressures (mmHg) S/D (mean)*	*Left ventricular pressure systolic (mmHg)*
Basal	90	1·1	103/49 (67)	140
45 mg	95	1·4	110/60 (74)	134
90 mg	95	1·4	112/57 (76)	134
180 mg	113	1·6	117/61 (81)	137

With the 300 mg injection the patient coughed, developed generalised seizures, ventricular tachycardia, and hypotension unresponsive to immediate resuscitation, including adequate ventricular pacing and pressor agents. Necropsy confirmed the diagnosis of primary (plexigenic) pulmonary hypertension.

Diazoxide administered by peripheral vein has been found to lower pulmonary artery pressure and resistance in patients with pulmonary hypertension (Just and Stein, 1969). The intravenous solution is highly alkaline (pH 11·6) and known to be irritating to vascular tissue. Given the potentially lethal response to pulmonary artery injections in patients with primary pulmonary hypotension (Snider *et al.*, 1973), we wonder if pulmonary artery injection should be avoided in future trials of this drug.

Finally, our patient had a pro
pulmonary artery pressures at lov
the diazoxide binding capacity of
normal serum albumin is 160 mg
Koch-Weser, 1973), the 300 m
ably results in a sudden large
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be interested to learn if the
Wang *et al.* showed progress
lower doses. If so, the patt
predict whether the 300 mg
beneficial or hazardous.

Joseph Michael Ru
John S. Schroeder,
Stanford Universit
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Wirkung von Diazoxid, einer neuen
Substanz, auf den grossen und den
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Snider, G. L., Ferris, E., G
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Primary pulmonary hypertens
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This letter was shown
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Sir,

Drs Rubino and Schroeder
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F., Ahamad, R., and
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at least as strong a vasodilator at arteriolar level as diazoxide. We have no experience in the use of this drug and we do not know, therefore, whether failure to respond to nitroprusside necessarily predicts failure to respond to diazoxide but it may well be so.

Drs Rubino and Schroeder are correct in stating that the 300 mg injection will lead to a temporary large increase in the level of unbound diazoxide. This, however, is not necessarily disadvantageous providing the trend up to that point had been favourable.

Primary plexigenic pulmonary hypertension is a highly lethal condition and such patients tolerate any invasive investigation badly. The proportion helped by diazoxide may be small but it seems to us essential that the drug is fully and carefully evaluated. Despite the risks of invasive investigations in such patients we believe that haemodynamic evaluation of the probable response is essential if oral maintenance treatment is being contemplated.

E. G. Wade and D. J. Rowlands,
The Department of Cardiology,
The Royal Infirmary,
Manchester.

British Heart Journal, 1979, **42**, 364–365

Anticoagulants and the Björk-Shiley pros

Sir,
We read this paper with great interest (*British Heart Journal*, 1978, **40**, 558–562). Long-term anticoagulation is associated with the risk of bleeding and to an extent enforces restriction on the quality of life of the patient (*British Medical Journal*, 1978). In addition there is a risk, though small, of thrombosis in spite of adequate anticoagulation. In view of this we feel that it is important to look for alternatives to long-term oral anticoagulants. However, there are several important points in your study that require careful consideration before drawing any conclusions. Dipyridamole has been started on day 3; it is well documented that platelets become 'stickier' in the immediate postoperative period, and by day 3 platelets may have already become attached to the valves. In the absence of anticoagulation the platelet plugs may be stabilised by thrombin generation and clot formation.

We have shown that dipyridamole when used clinically has to attain an optimum blood level of 3·5 μmol/l (range 2 to 5 μmol/l) to produce an adequate antiplatelet effect (Rajah *et al.*, 1977). There is no indication in the study that any blood level or platelet functions had been done on any of the patients in the dipyridamole group before discharge from hospital. It has been our experience that on a dose of 150 mg daily most patients did not attain optimum blood levels and platelet functions were not inhibited. This implies that in your study most of the patients in the dipyridamole group were in no way protected after valve replacement.

Before embarking on the use of antiplatelet drugs alone in this clinical situation we feel that it is necessary to extend the findings of Sullivan *et al.* (1971). Here it was clearly shown that the dipyridamole and warfarin group combined was superior to warfarin alone, but the limitation of that trial was that a number of patients dropped out of the trial because of the side-effects of dipyridamole. We have been conducting a similar trial to that of Sullivan *et al.* for the past 4 years; the dose of dipyridamole is determined by its blood level and/or platelet functions routinely. We confirm the superiority of dipyridamole and warfarin over warfarin in patients with the Starr-Edwards, Björk-Shiley, and Lillehei-Kaster valves, and in addition the drop-out of patients because of the side-effects of dipyridamole is negligible.

If dipyridamole alone is to be used in a trial, we suggest starting it
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period, and orally when
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British Medical Journal (19
1, 1505–1506.
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Watson, D. A. (1977).
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Sullivan, J. M., Harken,
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This letter was shown
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Sir,
It is well document
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t Sullivan *et al.* (1971) showed
nd warfarin combined were
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ts dropped from the trial because of undesirable side-effects of dipyridamole. We were interested to learn that the Leeds group had confirmed the findings of Sullivan *et al.* (1971) in patients with varying types of prosthetic valves and await this publication.

We note the recommendation that if dipyridamole is to be used alone it should be started preoperatively and continued intravenously immediately postoperatively. However, do this group have trial data regarding groups of patients treated with dipyridamole pre- and perioperatively compared with dipyridamole started postoperatively to support their recommendation, and also their suggestion that platelets become adherent to prosthetic valves in the first 3 days postoperatively? We acknowledge the caution concerning the intravenous use of dipyridamole in patients with hypotension and add that a considerable number of patients undergoing valve replacement return to the Intensive Care Unit conspicuously hypotensive.

M. G. St. John Sutton,
P. J. Oldershaw,
G. A. H. Miller, and
M. Paneth.

Notice

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tors should note that, in future, references in the text of
ubmitted to this journal and in the bibliography should
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ils of this new, uniform style, which was agreed at a
f the International Steering Committee of Medical
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532–35) and *Ann Intern Med* (1979; **90**: 95–9). Reprints
cle are available from the *Br Med J* (price 50p).

British Heart Journal, 1979, **42**, 366

The Remler M2000 semi-automatic blood p recorder

Sir,

The Remler M2000 semi-automatic blood pressure recorder together with the M3000 decoder have recently become available and provide a method of obtaining home blood pressure readings. While using it, however, we gained the impression that it recorded substantially higher blood pressures than those measured using conventional sphygmomanometers in our clinic. We, therefore, tested the accuracy and reliability of the Remler system against the London School of Hygiene (LSH), and Hawksley Random Zero (RZS) sphygmomanometers, as well as direct intra-arterial readings, together with a general practice based evaluation.

Firstly, we connected a Remler recorder and a conventional mercury manometer via a t-tube to a single cuff wrapped round a bottle. We were able to show that the calibration marks on the Remler print-outs were exactly at the correct level of blood pressure read on the mercury manometer.

The results of our comparison of Remler recordings with those with the LSH, RZS, and intra-arterial blood pressure levels are shown in the Table. The LSH study was taken with blood pressures in 14 subjects measured in the same arm as the Remler, with a t-tube attachment as above. The RZS study was conducted along similar lines to that of Ramsay *et al.* (1977); blood pressures being measured in opposite arms by two observers who alternated machines. Ther for differing blood pressure e arms or between observers, bu to higher readings from the Ren differences could not be account tendencies to record blood pr or fifth diastolic phases. Remler recordings and ir measured in opposite ar

Table *Mean systolic and diastolic blood pressure measured using Remler M2000 recorder in comparison with London School of Hygiene, Random Zero sphygmomanometer, and direct intra-arterial readings*

	Blood pressure (mmHg) *Systolic*	*Diastolic Phase 5*
Remler	166·5	115·1
LSH	159·1*	104·7*
Remler	145·6	93·4
RZS	137·2†	85·3*
Remler	170·9	107·0
Intra-arterial	159·5†	80·9*

* P < 0·001; † P < 0·01.

We have further teste Remler machine in genera to obtain 544 home bloc microcassettes in 9 we decoding, only 276 readin interpreted from the print-out reason for inability to obtain r calibration artefacts obscurin not from failure to obtain beats by unsatisfactory at phone over the brachial ar

While the Remler blood system has many attractions, ment should be encouraged its use in view of the cor unreliability.

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British Heart Journal, **42**, 367–368

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sarcoidosis with refractory ventricular dia and heart failure

interest the recent case report of
Heart Journal, 1978, **40**, 931–933).
tly seen 2 patients with sarcoidosis
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premature beats. In view of these findings, we intend to discontinue steroid therapy and to treat her with beta-blockers.

Although we cannot be absolutely certain that neither of our patients has localised myocardial sarcoid infiltration, we feel that our extensive investigations make it unlikely and we now regard these cardiac abnormalities as coincidental with sarcoidosis. In view of the similarities between our cases and that of Walsh (1978), we think that more extensive investigations such as echocardiography or cardiac catheterisation with coronary angiography and cardiac biopsy should be undertaken before cardiac abnormalities in patients with sarcoidosis are attributed to myocardial involvement. This is particularly important, firstly because long-term steroid treatment may lead to a steroid cardiomyopathy, and secondly because there is some evidence to suggest that steroid treatment in myocardial sarcoidosis may increase the risks of development of ventricular aneurysm (Roberts *et al.*, 1977).

N. McI. Johnson, M. W. McNicol,
and D. J. Coltart
Cardiothoracic Department,
Central Middlesex Hospital,
London, NW10; and
Cardiac Department,
St Thomas' Hospital, London SE1.

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Johnson, N. McI., Martin, N. D. T., and McNicol, M. W. (1979). Sarcoidosis presenting with pleurisy and bilateral pleural effusions. In the press.

Roberts, W. C., McAllister, H. A., jun, and Fertans, V. J. (1977). Sarcoidosis of the heart. A clinico pathological study of 35 necropsy patients and review of 78 previously described necropsy patients. *American Journal of Medicine*, **63**, 86–108

This letter was shown to Dr Walsh who replies as follows:

Sir,

In their letter Johnson *et al.* comment on the similarity of their patients to mine. The patient I reported on was remarkable for the variety of cardiac disturbances and arrhythmias, including recurrent refractory ventricular tachycardia and fibrillation, and the development of heart failure; the paroxysmal rather than the persistent nature of these abnormalities was commented on. Refractory ventricular tachycardia has previously been described in patients with cardiac sarcoidosis but is an uncommon phenomenon in reversible cardiac disease other than acute myocardial infarction or drug intoxications.

The first case of Johnson *et al.* had negative endomyocardial biopsies. Cardiac sarcoidosis may be lethal even when the lesions are localised, for example in the conduction pathways. In a patient with only mitral regurgitation as a clinical and angiographic finding, I would be very surprised if endomyocardial biopsy were positive; failure to find granulomas does not deny the validity of their clinical suspicions. The value of cardiac biopsy is in the diagnosis of *diffuse* disease of the heart.

In their second patient, they do not describe the extensive investigations carried out, but refer only to echocardiography. This investigation in the patient I reported.

For the clinician the situation in a p I described is straightforward; whe refractory life threatening rhythm d heart failure, one cannot withhold t might be beneficial. I hope that the up of such patients by Fleming a provide information concerning the less seriously affected patients.

Michael J. Walsh,
Wadsworth Hospital Cen
UCLA School of Medicin
Wilshire and Sawtelle B
Los Angeles,
California 90073
USA

amiodarone in bradycardia-tachycardia ıe

with interest the experience of
l co-workers (*British Heart Journal,*
1152) with amiodarone in the treat-
ick sinus syndrome. In the initial
isease bradycardia may be transient,
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isk of a further deterioration

osse and
ez Zuelgaray,
f Cardiology and National
rdiac Arrhythmias,
tex' National Hospital,
gentina.

This letter was shown to the authors who reply as follows:

Sir,

We treated patients with the bradycardia-tachycardia syndrome only, and we specifically excluded other patients with sinuatrial disease. Though bradycardia was usual in patients receiving amiodarone, 2 of the patients from our series are still using the drug successfully, without symptomatic bradycardia, $4\frac{1}{2}$ and $2\frac{1}{2}$ years later. We have used amiodarone in 3 further patients with the syndrome of alternating bradycardia and tachycardia; 2 responded well but the drug was withdrawn in the third patient because of syncope associated with excessive cardiac slowing. Three of the patients in our series belong to the group of patients in whom bradycardia usually follows a bout of tachycardia but the abnormal rhythms were clearly independent in the other 2 patients. I agree that rational treatment of the bradycardia-tachycardia syndrome could follow division into categories on the lines proposed by Dr Posse and Dr Zuelgaray. Their interesting suggestion deserves study with a larger group of patients.

A. K. Brown,
Department of Medicine,
Royal Lancaster Infirmary,
Lancaster LA1 4RP.

British Heart Journal, 1979, **42**, 370–371

A co-operative trial in the primary preventio ischaemic heart disease using clofibrate

Sir,
We read with great interest the recent report from the Committee of Principal Investigators on the co-operative trial in the primary prevention of ischaemic heart disease using clofibrate (*British Heart Journal*, 1978, **40**, 1069–1118).

We note with satisfaction that our dietary prevention trial in two mental hospitals near Helsinki (Miettinen *et al.*, 1972) was considered by the Principal Investigators in their Discussion. However, the results of our study were partly misrepresented.

On page 1101 it is stated, correctly, that 'there was a significant reduction in IHD mortality' during the experimental diet periods. However, on page 1096 the authors say that 'mortality from IHD, . . . , was not reduced in . . . primary prevention trials using a diet rich in polyunsaturated fats (. . . ; Miettinen *et al.*, 1972)'. This statement is in obvious contradiction to the previous one and is false.

On page 1098 it is stated that in our study (Miettinen *et al.*, 1972) there was 'a non-significant excess in total mortality among the experimental group taking a polyunsaturated fat diet'. This is not true. On the contrary, in our trial total mortality among the experimental groups was not higher but lower than among the control groups. The relevant mortality figures per 1000 man-years were as follows (cf. Table 6, loc. cit.):

	Hospital N	*Hospital K*
Experimental diet period	34·56	35·12
Normal diet period	38·78	40·20

Thus in both hospitals total mortality was reduced during the experimental diet periods. The differences, however, failed to reach statistical significance.

On page 1101 the authors refer to the criticisms of our study by Halperin *et al.* (1973) but, curiously enough, completely ignore our reply (Miettinen *et al.*, 1973). In this reply we showed that the remarks of Halperin and his colleagues were largely unfounded.

On page 1099, where the aut
study of Sturdevant *et al.* (197
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high in polyunsaturated fat, it
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1976) with the finding that the p
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Matti Mietting
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Department
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Effect of diet on corona
2, 438–439.
Miettinen, M., Turpeinen,
and Paavilainen, E. (1972)
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Lancet, **2**, 835–838.
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and Paavilainen, E. (1973). Effect
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Miettinen, M., Turpeinen, O., K
E., and Elosuo, R. (1976). P
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diet. *Annals of Clinical Rese*
Sturdevant, R. A. L., Pearce
Increased prevalence of
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Medicine, **228**, 24–26.

This letter was show
who reply as follow

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Notices

British Heart Journal, 1979, **42**, 372

International Society and Federation of Cardiology

The following meetings will be held under the auspices of International Society and Federation of Cardiology:

6 to 9 November 1979, Houston, Texas, USA: *5th International Congress of Atherosclerosis* (Inquiries: D. A. M. Goto, Dept. of Med., Baylor College of Medicine, the Methodist Hospital, 6516 Bertner Avenue, Mail Station A 601, Houston, Texas 77030, USA.)

9 to 10 November 1979, Budapest, Hungary: *Symposium on Cardiomyopathies* (in collaboration with the World Health Organisation, with the Hungarian Society of Cardiology, and the Hungarian Society of Pathology) (Inquiries: Dr Lagos Matos, Hungarian Institute of Cardiology, PO Box 9/88, Budapest, Hungary.)

The Young Researcher Prize

The European Society of Cardiology announces the award 'Le Prix du Jeune Chercheur' ('The Young Researcher Prize') on the occasion of the VIII European Cardiology Congress. It will be given for research work on cardiovascular biology, investigative techniques, and medical o
of treatment in the cardiovascula

The award will be Fr.100 000.

Competitors must be Europea
years of age on 1 January 1980

A selection committee and a
will select four papers which
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the congress. Entries
1 February 1980. (Text a
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The prize money is be
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**The Second Pan Ameri
Diseases of the Chest** wil
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Requests for further infor
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Congress on Diseases of the C
Rio de Janeiro, RJ 20000, Br

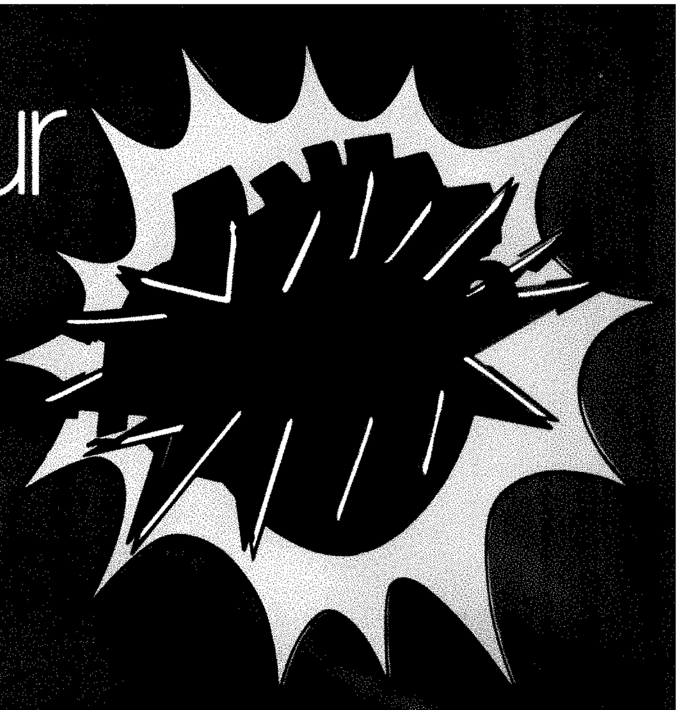
olleagues are correct in their mortality but the point which is that the degree of apparent *ry heart disease* mortality was eater than that for overall g, therefore, that a slight excess ed in mortality from *non- s.* Indeed, it is relevant to d on page 1098: 'Age-adjusted person-years for malignant diet v 3·96 control) and 'other et v 13·03 control) were both eiving the cholesterol-lowering inal excess of non-cardiovascular ki Mental Hospitals Study emphasis in view of the cardiovascular mortality y.

e Los Angeles Veterans Administration Study, where increased mortality from non-cardiovascular causes is also evident when deaths from atherosclerotic events are subtracted from total death figures. This adds support to the findings of the WHO study.

Finally, the question of the degree to which a diet high in polyunsaturated fat is lithogenic will become increasingly clear as more studies are reported. One interesting aspect of the study by Sturdevant *et al.* (1973) is that lithogenicity increased with the number of consumed meals rich in polyunsaturated fats. The negative findings of Miettinen *et al.* (1976) need not be in conflict with those reported by Sturdevant *et al.* (1973), since there is no reason to assume that diets, differently enriched in polyunsaturated fats with different P/S ratios, will all have the same degree of lithogenicity or non-lithogenicity.

Committee of Principal Investigators

Are all your patients under control?



You could have more Adalat patients than you think. There are many angina patients on nitroglycerin or beta-blockers who are still suffering several attacks a day. They believe that life is as good as it is likely to be and rarely complain.

U.K. clinical experience[1] confirms that a prescription for Adalat, alone or in combination, could markedly reduce the number of attacks and improve exercise tolerance.

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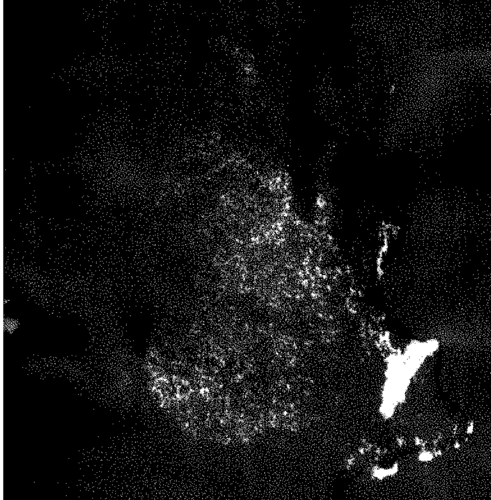
2. Heart work load is reduced.
3. O_2 supply to the myocardium is increased.



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Presentation Orange, soft gelatin capsule containing yellow viscous liquid. Each capsule contains 10mg nifedipine. **Uses** *Mode of Action* Adalat is a potent calcium antagonist. Its most important effect is to protect the heart against excessive oxygen utilisation during physical activity. There is a reduction in cardiac work and in myocardial oxygen demand. Adalat also causes peripheral vasodilatation and thus reduces peripheral resistance and heart work load. Adalat has no therapeutic anti-arrhythmic effect. Since Adalat does not [illegible] rise in intraocular pressure, it can be used in patients with glaucoma. [illegible] For the treatment and prophylaxis of angina pectoris. **Dosage and Administration** For oral administration, the capsules should be take[illegible] little fluid during or after meals. The recommended dose is one 10mg capsule [illegible] three times daily may be [illegible] in the mouth. **Contra-indications** Must not be given to women [illegible] of child-bearing. **Warnings and Precautions** Adalat is not a [illegible] blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker, preferably over 8-10 days. Adalat may be used in combination with beta-blocking drugs and other antihypertensive agents, but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Adalat will not prevent possible rebound effects after cessation of antihypertensive therapy. Adalat should be used with caution in patients whose cardiac reserve is poor. Ischaemic pain has been reported in some patients, commonly within 30 minutes of the introduction of Adalat therapy. Patients experiencing this effect should discontinue Adalat. The use of Adalat in diabetic patients may require adjustment of their control. There is no known [illegible] These are transient and invariably disappear with continued treatment. **Overdosage** Standard measures such as atropine and noradrenaline may be used for resultant bradycardia and hypotension. Intravenous calcium gluconate may be of benefit. **Pharmaceutical Precautions** The capsules should be protected from strong light and must be stored in the manufacturer's original container. **Legal Category** POM. **Pack Quantities and Basic NHS Cost** Adalat is available in foil packs of 100 capsules. Daily treatment cost 33p (3 capsules ex 100). **Further Information** Nil. **Product Licence Number** PL0010/0021; Republic of Ireland PA 21/3/1.

Additional prescribing information on Adalat (nifedipine) is available from:
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Haywards Heath, West Sussex RH16 1TP.

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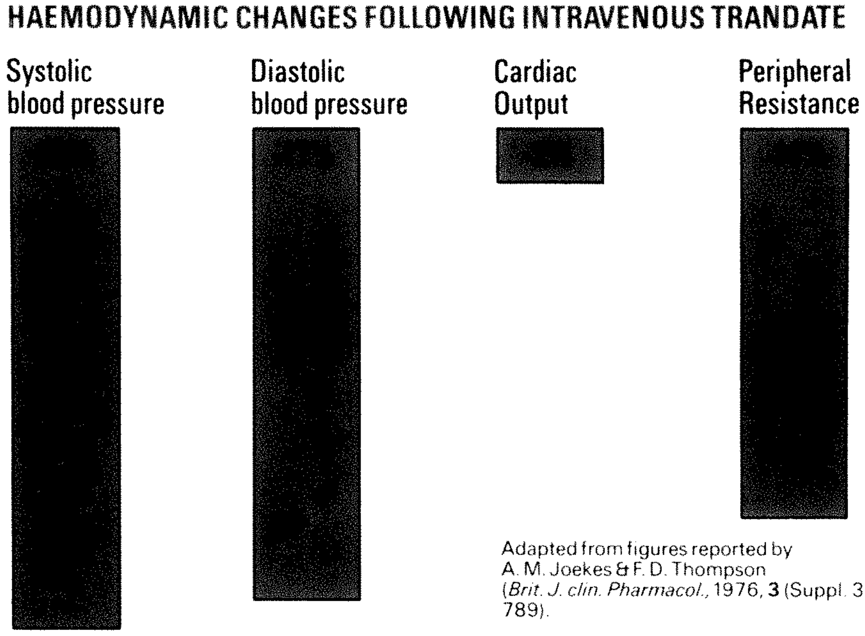

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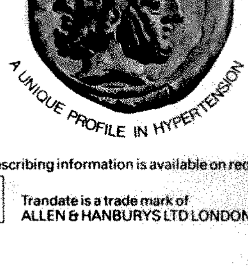

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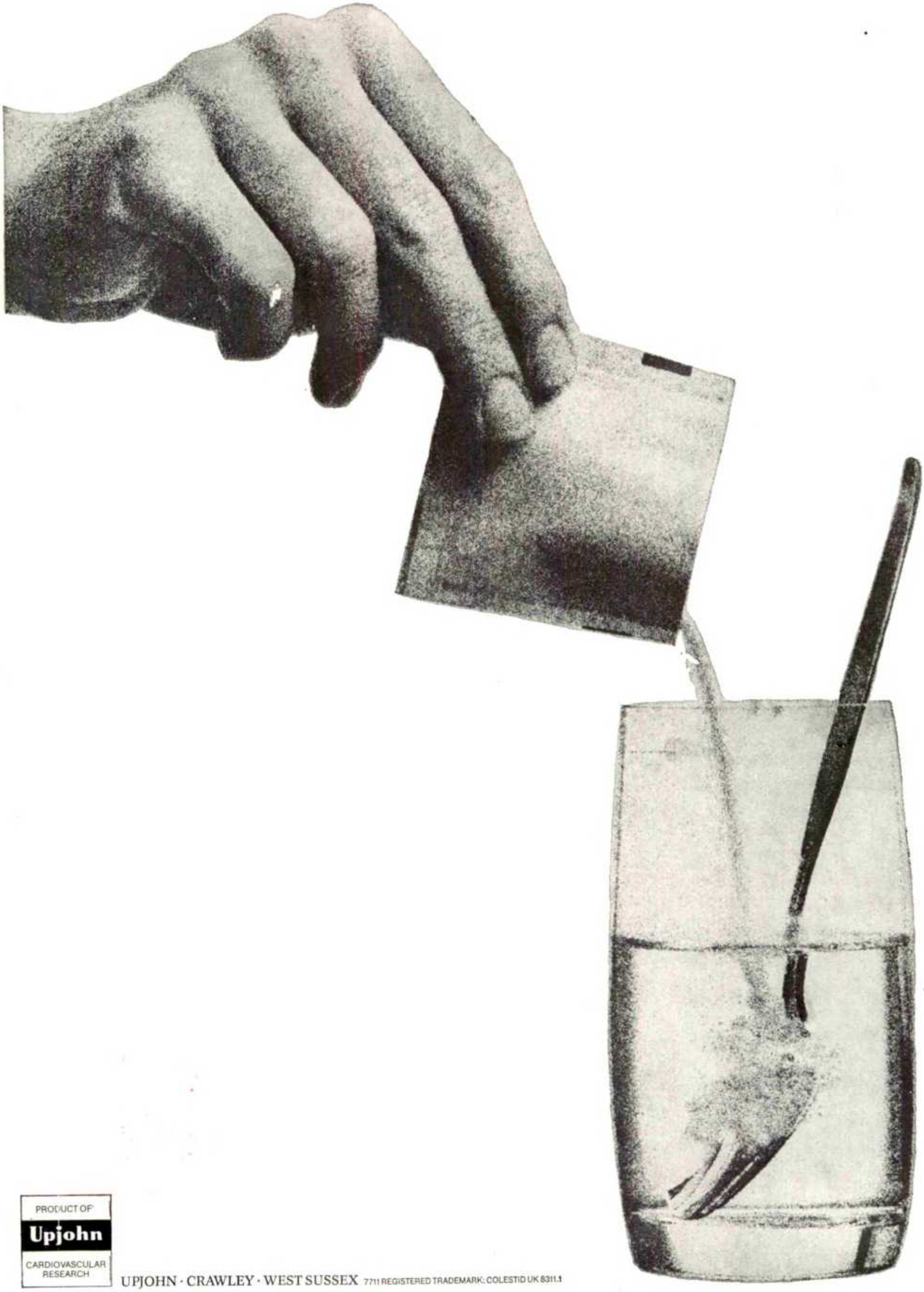

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References: 1. Med. J. Aust. (1973). *1*:1223.
2. JAMA (1972). *222*:676.
3. New Zealand J. Med. (1972). *76*:12.

Prescribing Information

Presentations: Tasteless and odourless granules of colestipol hydrochloride. *Uses:* Adjunctive therapy to diet for treatment of hypercholesterolaemia, particularly Frederickson Type II. *Dosage and Administration:* Always mix with water or other fluids before ingesting. Oral total daily dosage for adult 15–30 grams. Take in divided doses 2–4 times daily. *Contraindications:* Hypersensitivity to colestipol. *Precautions, Warnings:* Not to be taken in dry form. Colestid may interfere with absorption of some drugs (e.g. penicillin G, tetracycline, chlorothiazide). Safety for use in pregnant women or children not established. *Package Quantities:* 30 x 5 g sachets; 250 g bottle. Each sachet or scoopful contains 5 g colestipol hydrochloride. *Further Information:* Colestid is not absorbed. It binds bile acids causing further cholesterol conversion to bile acids thus lowering serum cholesterol levels. *Basic NHS Costs:* 30 x 5 g sachets £8.90. 250 g bottle £13.76. Product Licence Nos. PL 0032/0055. PL 0032/0057. *Full Product information is available on request.*

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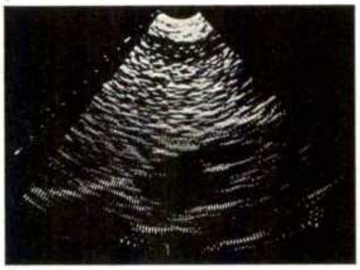

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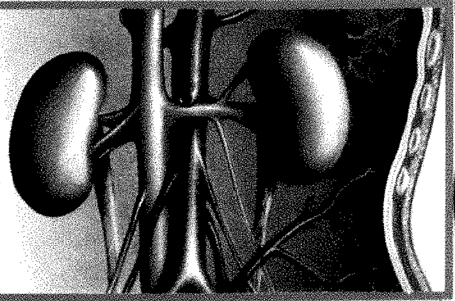

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British Heart Journal, 1979, **42**, 373-380

Aggregation of coronary risk factors in families of men with fatal and non-fatal coronary heart disease

AILA M. RISSANEN AND ESKO A. NIKKILÄ

From the Third Department of Medicine, University of Helsinki, Helsinki, Finland

SUMMARY The occurrence of main coronary risk factors was assessed in the families of 211 men under age 56 from East Finland. Fifty men were survivors of a recent myocardial infarction, 55 had died of myocardial infarction, 53 suffered from uncomplicated angina, and 53 were healthy reference men. Familial hyperlipidaemia was twice and familial hypertension three times as common in case as in reference families; other risk factors were equally common in both. Familial hypercholesterolaemia was commonest in the families of men with fatal myocardial infarction, and multiple type familial hyperlipidaemia in those of men with angina. Any increase in familial aggregation of coronary heart disease was invariably paralleled by increased aggregation of hyperlipidaemia and hypertension, with the most impressive aggregation of both traits in case families with a maternal history of early coronary death. It is concluded that most of the familial aggregation of coronary heart disease is mediated by familial aggregations of hyperlipidaemia and hypertension.

Coronary heart disease, particularly when presenting early in life, tends to run in families (Slack and Evans, 1966; Phillips *et al.*, 1974; Rissanen, 1979a, b). Some of this familial predisposition is mediated by familial resemblance in the major risk factors, such as hyperlipidaemia, hypertension, and diabetes. It is not known, however, how much of the familial component of the disease is accounted for by these risk factors. While some investigators have suggested that these factors alone may be responsible for all the familial trends observed (Stamler, 1973; Keys, 1975), others have concluded that most of these trends must be the result of factors as yet unidentified (Epstein, 1967a).

In the present investigation, the occurrence of coronary heart disease and its major risk factors have been recorded in the families of relatively young men from North Karelia, East Finland, where the incidence of premature coronary heart disease is the highest in the world (Epstein and Krueger, 1969). A previous report (Rissanen, 1979a) showed that coronary heart disease in this area has pronounced familial tendencies.

The present report represents an attempt to relate the familial trends of the disease to the occurrence of its major risk factors. Such information may help in improving the prospects of prevention of premature coronary heart disease in endemic areas.

Received for publication 23 March 1979

Subjects and methods

INDEX CASES

The index cases of the study were 211 men under age 56 from two neighbouring communities in North Karelia. Fifty of these men had had a non-fatal and 55 a fatal myocardial infarction, 53 suffered from uncomplicated angina pectoris, and 53 were healthy reference men.

The 50 men with non-fatal myocardial infarction and 55 men who died were the consecutive men in the study communities who suffered non-fatal (survival 28 days or more) or fatal (survival less than 28 days) myocardial infarction in 1972 to 1974. The cases with angina pectoris were screened from occupational health examinations in local paper mills. The selected subjects had both an abnormal electrocardiogram at rest (Minnesota Code Nos. 1·2–3, 4·1–3, 5·1–2, 6·1–2, 7·1–2, or 8·3) and classical anginal chest pain, but no history of myocardial infarction. The reference or control were free of any symptoms of coronary heart disease and had no signs of ischaemia in the resting electrocardiogram. They were selected from the same employee rosters as the patients with angina pectoris, with whom they were matched for age and occupation. Details of the selection process have been given earlier (Rissanen, 1979a).

The age distribution was similar in the four study groups. The average age was 48·1 years (range 22 to 55 years).

The medical records of the index cases were carefully reviewed. All living men and 148 spouses were examined by A.R. They were also interviewed by a psychologist and a dietitian as to their habits both before and after the diagnosis of coronary heart disease in the patient. Most patients had modified their habits temporarily after the diagnosis of coronary heart disease was made, but permanent changes were rare, except for smoking. One-quarter of the smokers had stopped smoking and another quarter had cut down their consumption. The mean change in weight since the first diagnosis of coronary heart disease was approximately +1·5 kg. The average intake of fat of the patients, estimated by the dietary recall method, was 137 g/d, 80 per cent of which was saturated animal fat.

A blood sample was obtained from the living men and all spouses. They were asked to maintain their customary diet, to abstain from alcohol, and to fast overnight (12 hours) before sampling. Hypolipidaemic drugs were discontinued two weeks before sampling. Acutely ill subjects were rescheduled. No samples were drawn during the first three months after the acute myocardial infarction.

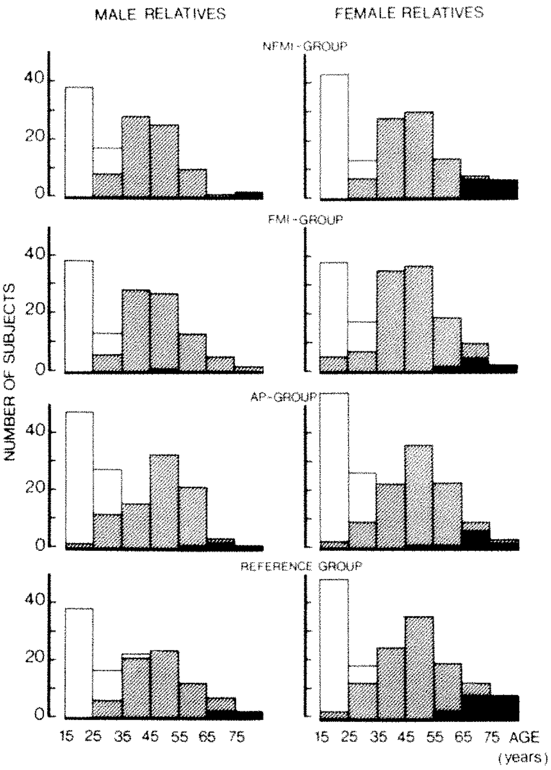

Fig. *Age distribution of the study participants.* ☐ *children,* ▨ *sibs,* ■ *parents. FMI, fatal myocardial infarction; NFMI, non-fatal myocardial infarction; AP, angina pectoris.*

Table 1 *Number of participants in different study groups*

Study group	*Non-fatal myocardial infarction*	*Fatal myocardial infarction*	*Angina pectoris*	*Reference*
Index cases	50	55	53	53
Fathers	2	1	4	5
Mothers	14	9	10	17
Brothers	69	78	81	65
Sisters	75	104	94	93
Sons	46	46	63	50
Daughters	48	43	68	58
Total relatives	254	281	320	288

RELATIVES

The index cases were reported to have 522 deceased and 1280 living relatives aged 15 or over. The living relatives were sent a questionnaire that included questions on history of disease, physical complaints, medication, as well as on smoking and dietary habits. The relatives were also asked to report to local medical laboratories, where a blood sample was drawn after an overnight fast, and height, weight, and resting electrocardiogram were recorded. The laboratories had been instructed to help the respondents in filling in the questionnaire, which together with the serum sample and the recorded data was then forwarded to Helsinki for analysis.

Of the living relatives, 1143 (89·3%) complied with the study. The number of participants in different study groups is shown in Table 1. The age distribution of the relatives was similar in all groups (Fig.). The mean age of both the brothers and sisters was 47·0 years, and that of the children 19·3 years.

The reliability of the questionnaire reports was evaluated by checking the information from 350 questionnaires against the records of hospitals and private physicians. The reported diagnoses of hypertension and diabetes could invariably be confirmed for the cases in which treatment for the ailment was also described. Therefore, the diagnoses of these diseases were accepted as reported if the treatment was also mentioned. All the reports of diagnosed coronary heart disease were, however, checked from earlier medical records or from death certificates.

To obtain information on changes in life style which the disease in the family might have caused, a sample of 145 relatives was invited to an interview and a clinical examination. Ninety-one per cent of them responded and were examined. Many relatives of the affected index cases expressed increased concern about their health, but actual changes in the habits of symptom-free subjects were negligible. Only the relatives who themselves had clinical coronary heart disease had modified their habits to a similar extent as the affected cases. When checked against the symptoms reported at the interview, the questionnaire reports on symptoms such as chest pain proved to be too unreliable for analysis.

METHODS OF DATA ANALYSIS

Serum cholesterol was determined by the method of Huang *et al.* (1961), and serum triglycerides by an autoanalyser according to Kessler and Lederer (1965). The coefficient of variation of the determinations during the two-year period of the study did not exceed 3 per cent. To minimise the effect of seasonal variation (Aromaa *et al.*, 1975), sampling was discontinued for the summer months. All lipid values were adjusted to age 45 using regression equations derived from a large Finnish population study (Aromaa *et al.*, 1975). The point for definition of hyperlipidaemia was set at the 90th centile of the age-adjusted values of the reference relatives. The limits are 8·81 mmol/l (340 mg/100 ml) for serum cholesterol in both sexes, and 2·31 mmol/l (205 mg/100 ml) and 1·70 mmol/l (150 mg/100 ml) for serum triglycerides in men and women, respectively.

The criteria for familial aggregation used in this study were as follows: familial hyperlipidaemia was considered to be present when at least 30 per cent (and a minimum of two) of the relatives of the index case had hyperlipidaemia. The familial hyperlipidaemias were classified as hypercholesterolaemia (type II familial hyperlipidaemia), hypertriglyceridaemia (type IV familial hyperlipidaemia), or multiple type (combined) hyperlipidaemia according to the predominant type of hyperlipidaemia in the family members. The term familial hypertension was used when at least 30 per cent (and a minimum of two) of the adult relatives of the index case had a treated hypertensive disease.

Qualitative data were analysed by the χ^2 test. For quantitative data, Student's t test was used. Since the values of the members within a family are not independent of each other, significance tests will have to be interpreted as rough estimates of strength of association between the variables.

The groups with non-fatal myocardial infarction, fatal myocardial infarction, and angina pectoris will often be referred to jointly as case groups in the following text.

Results

FREQUENCY OF RISK FACTORS AMONG THE INDEX CASES

The serum cholesterol and triglyceride levels of the patients with non-fatal myocardial infarction and angina pectoris were remarkably higher than those of reference men (Table 2). Hypercholesterolaemia and hypertriglyceridaemia were three to four times as common among patients as among the reference men and all the other main coronary risk factors, with the exception of overweight, were significantly more common among case than reference men (Table 3). Most notably hypertension was six times more common among the patients than the reference men. There were no appreciable differences in the prevalence of any of the risk factors between the patients with non-fatal myocardial infarction and those with angina pectoris.

Table 2 *Mean levels of serum lipids and frequency of hyperlipidaemia* in members of different study groups*

		Serum cholesterol (mean ± SD, mmol/l)	*Serum triglycerides (mean ± SD, mmol/l)*	*Hyper-cholesterolaemia** (%)	*Hyper-triglyceridaemia** (%)
Index cases	Non-fatal myocardial infarction	7·77 ± 1·57†	1·95 ± 1·49†	32·0‡	32·0‡
	Angina pectoris	7·55 ± 1·67†	1·84 ± 0·88†	30·2‡	20·8†
	Reference	6·95 ± 1·23	1·44 ± 0·65	11·3	7·5
Brothers	Non-fatal myocardial infarction	7·71 ± 1·29†	1·73 ± 0·98	26·1†	17·4
	Fatal myocardial infarction	7·48 ± 1·61	1·69 ± 1·04	25·6†	18·0
	Angina pectoris	7·24 ± 1·49	1·61 ± 1·15	17·3	17·3
	Reference	7·21 ± 1·34	1·49 ± 0·70	12·3	12·3
Sisters	Non-fatal myocardial infarction	7·35 ± 1·99	1·23 ± 0·60	12·0	13·3
	Fatal myocardial infarction	7·57 ± 1·66†	1·31 ± 0·61	21·1†	18·3
	Angina pectoris	7·36 ± 1·45	1·50 ± 0·94†	12·8	30·9†
	Reference	7·03 ± 1·49	1·19 ± 0·56	7·5	11·8
Children	Non-fatal myocardial infarction	5·58 ± 1·00	0·90 ± 0·65	5·3	6·4
	Fatal myocardial infarction	5·94 ± 1·14	1·00 ± 0·50	12·4†	6·7
	Angina pectoris	5·73 ± 0·95	1·12 ± 0·70†	5·3	16·0†
	Reference	5·50 ± 0·95	0·91 ± 0·48	5·6	7·5

*Serum cholesterol ≧8·8 mmol/l (men and women)/serum triglycerides ≧2·3 mmol/l (men) or ≧1·7 mmol/l (women).
The values are adjusted to age 45.
†$P < 0·05$ between case and reference group.
‡$P < 0·01$ between case and reference group.

Table 3 *Frequency of main risk factors in case and reference groups (%)*

		*Hyperlipidaemia**	*Hypertension*	*Clinical diabetes*	*Relative weight ≧120*	*Regular smoking*
Index cases	Case	43·7‡	41·7‡	9·7	19·4	72·8†
	Reference	17·0	7·5	—	13·2	49·1
Brothers	Case	33·8	21·9	4·4	12·7	43·9
	Reference	23·1	13·8	—	10·8	40·0
Sisters	Case	32·6†	26·4	1·8	29·0	14·7
	Reference	16·1	20·4	2·2	26·9	14·0
Children	Case	10·2	1·6	—	4·5	29·9
	Reference	11·1	—	—	1·9	29·5

*Age adjusted serum cholesterol ≧8·8 mmol/l (men and women) and/or age adjusted serum triglycerides ≧2·3 mmol/l (men) or ≧1·7 mmol/l (women).
†$P < 0{\cdot}01$ between case and reference groups.
‡$P < 0{\cdot}001$ between case and reference groups.

FREQUENCY OF RISK FACTORS AMONG RELATIVES

Hyperlipidaemia

The serum lipid patterns of the relatives in the various case groups differed considerably from each other. The serum cholesterol levels of the brothers were only slightly higher than those of the reference brothers, but the serum cholesterol levels of the sisters of the patients with fatal myocardial infarction were very high (Table 2). Hypercholesterolaemia was twice as common among the sisters and children of these men as it was among the sisters and children in other case groups. The highest serum triglyceride levels, on the other hand, were found among the relatives of patients with angina pectoris (Table 2). Among the sisters and children of these patients, the rate of hypertriglyceridaemia was more than twice that of the corresponding relatives of men with non-fatal mycoardial infarction and those with fatal myocardial infarction. Among the latter relatives, the rate of hypertriglyceridaemia was similar to that among the reference relatives.

Though the overall differences in the rate of hyperlipidaemia between case and reference relatives were small, family clusters of hyperlipidaemia were much more frequent in the case than in the reference group (Table 4). Familial hyperlipidaemia was present in one-third of case families but in only one-sixth of reference families ($P < 0{\cdot}05$). Familial hypercholesterolaemia was the predominant abnormality in the group with fatal myocardial infarction, whereas familial multiple type hyperlipidaemia prevailed in other study groups.

Hypertension

Hypertension had been diagnosed in approximately one-fifth of the brothers and in a quarter of the sisters in all case groups (Table 3). These rates are 1·6 and 1·3 times the rates in the corresponding reference relatives ($P < 0{\cdot}05$). Familial hypertension was, however, almost three times as common in case families as in reference families, occurring in 34 per cent of case families and in 13 per cent of reference families ($P < 0{\cdot}05$).

Other risk factors (Table 3)

Clinical diabetes was present in 4 per cent of case brothers and in 2 per cent of both case and reference sisters. Overweight was equally common in case and reference relatives. Smoking habits were also similar in case and reference relatives. Diabetes, overweight, and smoking were equally common in the relatives of all case groups. None of these risk factors showed any distinct familial trends.

AGGREGATION OF RISK FACTORS IN RELATION TO FAMILIAL AGGREGATION OF CORONARY HEART DISEASE

Effect of parental history of coronary heart disease

There were 14 case families in which the mother of the index case had died of coronary heart disease before the age of 70. Hypertension and hyper-

Table 4 *Prevalence of familial hyperlipidaemia in different study groups*

Study group	*No. of families**	*Familial hyperlipidaemia*			
		Type II *Percent of families*	*Type IV*	*Multiple type*	*All types*
Non-fatal myocardial infarction	47	10·6	2·1	17·2	29·8
Fatal myocardial infarction	50	28·0†‡	2·0	14·0	44·0
Angina pectoris	53	3·8	5·7	20·7	30·2
Reference	46	4·3	4·3	6·5	15·1

*Families with a minimum of two participating relatives.
†$P < 0{\cdot}01$ between the fatal myocardial infarction and the other case groups.
‡$P < 0{\cdot}005$ between the fatal myocardial infarction and reference group.

Table 5 *Frequency of hypertension and hyperlipidaemia in case sibs according to parental history of coronary heart disease*

	No. of families	*Hypertension (%)*			*Hypercholesterolaemia (%)†*			*Hypertriglyceridaemia (%)†*		
		Patients	*Brothers*	*Sisters*	*Patients*	*Brothers*	*Sisters*	*Patients*	*Brothers*	*Sisters*
Mother died of coronary heart disease before age 70	14*	70·0‡	37·5‡	43·8‡	60·0	45·8‡	21·9	10·0	20·1	18·8
Father died of coronary heart disease before age 70	38*	56·2‡	29·9‡	26·9	26·1	17·9	22·4	30·4	19·4	17·1
Neither parent died of coronary heart disease before age 70	108	33·3	16·4	23·6	30·6	21·4	13·5	26·4	15·7	22·5

*Two families with parental history of coronary heart disease from both sides have been included in both categories.
†Age adjusted serum cholesterol ≧8·8 mmol/l (men and women).
Age adjusted serum triglycerides ≧2·3 mmol/l (men) or ≧1·7 mmol/l (women).
‡$P < 0{\cdot}05$ between the group with maternal/paternal history of coronary heart disease and the group without any parental history of coronary heart disease.

cholesterolaemia were very frequent in the offspring of these mothers (Table 5). Approximately one-half of their sons and daughters were hypertensive; one-half of the sons and one-fifth of the daughters also had hypercholesterolaemia.

The father of the index case had died of coronary heart disease before the age of 70 in 38 case families. Hypertension was somewhat more common in the offspring of these families than in the offspring of case families in which neither parent had died of coronary heart disease by age 70 (Table 5). A similar difference was not observed for hyperlipidaemia.

Hypertension and hyperlipidaemia were equally common in families with a parental history of fatal coronary heart disease over the age of 70 and in those without any parental history of coronary heart disease. The frequency of other coronary risk factors among the offspring was not related to parental coronary heart disease.

Effect of family clustering of coronary heart disease

Hyperlipidaemia and hypertension were very common among the sibs affected by coronary heart disease. One-half of the diseased brothers and two-thirds of the diseased sisters had hyperlipidaemia, and one-third of the brothers and three-quarters of the sisters were hypertensive. There was a gradual increase in the rates of these abnormalities among the unaffected sibs according to whether there were none, one, or several cases of coronary heart disease within the sibship. Thus, the symptom free sibs under age 45 in families with three or more affected sibs had, in the aggregate, 5·2 times more hypertension and 2·5 times more hyperlipidaemia than did the symptom-free subjects in families in which only the index case was affected ($P < 0{\cdot}01$ for both differences) (Table 6). Hypertension and hyperlipidaemia were equally common in young symptom-free subjects of all families with multiple affected sibs, irrespective of parental history of coronary heart disease. Of the 31 such families, familial hyperlipidaemia was present in 19 and familial hypertension in 18; both traits coincided in 11 of the families.

SPOUSE CONCORDANCE FOR RISK FACTORS

No significant correlations were found between the spouses for systolic or diastolic blood pressure levels, for serum cholesterol and triglyceride concentrations, or for relative body weights.

Discussion

Controversial views have been expressed concerning the causes of familial aggregation of coronary heart

Table 6 *Frequency of hypertension and hyperlipidaemia in symptom-free case sibs under age 45 according to family history of coronary heart disease*

	Hypertension (%)		*Hypercholesterolaemia (%)**		*Hypertriglyceridaemia (%)**	
Parental death from coronary heart disease before age 70	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*
No. of sibs with coronary heart disease in family (excluding index case)						
0	11·1	6·7	21·8	14·2	14·8	13·8
1	23·3	12·2	18·4	22·5	28·3	16·0
2 or more	37·5†	38·9†	33·3	18·8	33·3†	37·5†

*Age adjusted serum cholesterol ≧8·8 mmol/l. Age adjusted serum triglycerides ≧2·3 mmol/l (men) or ≧1·7 mmol/l (women).
†$P < 0{\cdot}01$ between the groups with no and 2+ affected sibs.

disease, itself a well-documented phenomenon (Slack and Evans, 1966; Phillips *et al.,* 1974; Rissanen, 1979a, b). Only a few studies have, in fact, proceeded beyond the point of merely establishing that such aggregation does occur.

From what is known it appears that high levels of serum cholesterol, blood pressure, and blood glucose play some—as yet undefined—roles in determining clustering of coronary heart disease within families (Deutscher *et al.,* 1969).

If these correctable risk factors were major causes of the familial pattern of coronary heart disease, such a disease pattern could perhaps be eliminated by early detection and appropriate treatment of the susceptible individuals. Such a possibility warrants special consideration in areas with high rates of premature coronary heart disease.

We have studied the extent and nature of familial aggregation of coronary heart disease in North Karelia, Eastern Finland, an area which has the world's gloomiest record of coronary heart disease morbidity. A previous article in this series (Rissanen, 1979a) confirmed the extraordinarily high overall rate of coronary heart disease in this area. It also described pronounced familial aggregation of coronary heart disease in the cohort of the present study.

The objective of the present report was to provide information about the risk factors associated with the familial aggregation of coronary heart disease observed previously. The results strongly suggest that most of this aggregation was attributable, or at least related to, familial aggregation of hypertension and hyperlipidaemia. Clustering of coronary heart disease within families was almost invariably accompanied by familial clustering of one of the two traits, or, when there was pronounced clustering of coronary heart disease, by distinct familial clustering of both.

The aggregation of these risk factors was most impressive in families in which the mother had died of coronary heart disease before age 70. There was considerable clustering of hypertension in all these families, in almost two-thirds accompanied by pronounced clustering of hyperlipidaemia. It is likely that the affected mothers possessed and passed to their offspring a set of potent determinants of early-onset hypertension and hyperlipidaemia. The present findings are consistent with those of a recent report from Norway which suggested that familial hypertension may be a major determinant of coronary heart disease in young women (Förde and Thelle, 1977). The importance of familial hypercholesterolaemia to coronary heart disease in women is also well documented (Slack and Nevin, 1968).

The overall rates of the traditional risk factors were not remarkable among the members of families in which the father had died of coronary heart disease before age 70. In fact, the clustering of coronary heart disease observed in these families appeared to some extent to exceed that expected on the basis of the prevalence of the major risk factors. If some of the clusters of coronary heart disease in these families had arisen from chance alone, and even if the failure to detect an excess of the major risk factors had in part been the result of methodological deficiencies, the possibility remains that in some of these families factors other than those studied here were responsible for the observed aggregation of coronary heart disease. A similar suggestion was put forward by the investigators in Tecumseh (Deutscher *et al.,* 1970). They concluded that any clustering of coronary heart disease in families of men who developed coronary heart disease past age 65 must be the result of factors as yet unidentified. Such possible predisposing factors include familial similarities in the structure of coronary arteries (Pesonen *et al.,* 1975), body build (McKusick, 1965), behaviour (Bortner *et al.,* 1970), smoking habits (Thomas, 1968), and in other shared environmental influences (Sholtz *et al.,* 1975).

There were some differences in the serum lipid profiles between the relatives of the various case groups. A pronounced excess of hypercholesterolaemia was found among the relatives of the index cases of fatal myocardial infarction, and a similar excess of hypertriglyceridaemia was detected among the relatives of the cases with angina. These variations in the lipid patterns may be related to the differences in the clinical patterns of coronary heart disease of the various case groups observed earlier (Rissanen, 1979a).

It was shown that predominantly fatal forms of coronary heart disease aggregated in families of the patients with fatal myocardial infarction, whereas uncomplicated angina was the predominant form of coronary heart disease in families of the patients with angina pectoris. It may therefore be postulated that hypercholesterolaemia favours the development of fatal coronary heart disease, whereas hypertriglyceridaemia mostly favours the development of angina. In support of this, several earlier studies have suggested that the serum cholesterol level is less strongly related to angina than to other clinical manifestations of coronary heart disease (Lawry *et al.,* 1957; Paul *et al.,* 1963; Chapman and Massey, 1964; van Buchem, 1967). It has also been reported earlier that the highest serum cholesterol levels tend to be associated with fatal coronary heart disease (Deutscher *et al.,* 1970; Tibblin *et al.,* 1975).

Once familial aggregation of the risk factors has been shown, the important issue is to decide whether this aggregation is caused by common genes or shared environmental influences. Though the present study was not designed to explore the aetiologies of the coronary risk factors, some limited observations on this issue can be made. First, the aggregation of hyperlipidaemia and hypertension in case families with a history of premature parental death from coronary heart disease suggests transmission by genetic factors. The rate of 50 per cent among the adult family members could hardly be explained otherwise. Second, environmental effects can be discounted as major causes of the familial trends observed, because there were no obvious similarities between spouses for any of the factors studied. Such similarities were found, on the other hand, within sibships even when the sibs lived far apart.

It is difficult, however, to disentangle genetic effects from familial environmental influences. Moreover, the response to environment may be genetically determined. A weak environmental effect may become a potent predisposing factor when superimposed on a susceptible phenotype. An interaction of genetic and environmental effects could thus account for most of the familial aggregation observed.

This kind of interaction could also explain the unusually high overall serum cholesterol levels of the study population. Finns, unlike most other populations studied, show a significant correlation between the dietary fat intake and the serum cholesterol level (Räsänen *et al.*, 1978). It is possible that the high serum cholesterol concentrations of Finns represent a genetically determined sensitivity to the typical Finnish diet, with its high content of saturated fat.

The impact of smoking should be viewed against the background set by the high serum cholesterol levels. Apart from the 'normal' Finnish serum cholesterol level, heavy smoking was the only major risk factor in one-third of the diseased index cases. We have also found earlier (Rissanen and Nikkilä, 1977) that smoking is an independent modifier of the development of coronary heart disease in the North Karelian families even in the presence of major familial risk factors.

The cross-sectional approach of comparing abnormality rates in first degree relatives of coronary patients with the rates in reference relatives is prone to several methodological deficiencies (Epstein, 1964). First, it is likely that the relatives of patients are more aware of the disease and therefore show excessive concern over health. However, it has been shown earlier (Honeyman *et al.*, 1968) that despite the concern shown, the relatives of coronary patients do little to improve their health. This fact could be verified also at the clinical examinations performed on the relatives of the present study. Second, a considerable bias may have been introduced by the selective removal from the study cohort of persons who died of premature coronary heart disease. Such persons are likely to harbour one or another of the major risk factors (Epstein, 1967b). Loss of brothers may have influenced the results. On the other hand, the mortality of sisters was still low, and thus not likely to be a major source of error.

LIBRARY

The findings of the present study have established that most of the familial susceptibility to coronary heart disease is mediated by familial aggregation of hypertension and hyperlipidaemia. An early detection and an appropriate treatment of these abnormalities would probably eliminate the risk and prevent or delay the subsequent development of the disease. Therefore, apart from active preventive efforts, relatives of patients with premature coronary heart disease should be submitted to close clinical surveillance for any emerging abnormality.

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Randomised multicentre trial of early mobilisation after uncomplicated myocardial infarction

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SUMMARY In a multicentre trial 742 patients in 13 hospitals in Wales were randomly allocated on the fifth day after uncomplicated myocardial infarction to be mobilised on the fifth or the tenth day. The trial shows no difference in first year mortality, nor in morbidity assessed after a median period of 13 months. Follow-up after one year suggests an unexplained lower mortality during the second and third years in the late mobilisation group.

The trend towards earlier mobilisation after myocardial infarction has been supported now by a number of retrospective studies (Brummer *et al.,* 1966) and controlled trials (Groden *et al.,* 1967; Harpur *et al.,* 1971; Lamers *et al.,* 1973; Royal Infirmary, Glasgow, 1973; Hayes *et al.,* 1974; Abraham *et al.,* 1975). Successive trials have shown a trend towards comparison of earlier mobilisation, starting with the trial of Groden and colleagues in 1967 which showed no adverse effect of mobilising at 15 compared with 25 days. Subsequent trials have likewise shown no disadvantage from mobilising at between 6 and 10 days compared with between 13 and 21 days (Harpur *et al.,* 1971; Lamers *et al.,* 1973; Royal Infirmary, Glasgow, 1973; Abraham *et al.,* 1975), the most meaningful being the relatively large Glasgow study of 538 patients mobilised at 7 compared with 14 days and reported in 1973 (Royal Infirmary, Glasgow, 1973). One more recent trial compared mobilisation at two days with mobilisation at nine days but follow-up of the 189 patients was very limited (Hayes *et al.,* 1974). In 1972, doctors in Wales were invited to collaborate in a multicentre randomised trial of mobilisation at five days compared with 10 days after uncomplicated myocardial infarction. We here report the results of this trial of 742 patients. The trial differs from previous trials in that it was of relatively early mobilisation and long follow-up, it involved more patients, and it was a multicentre trial with most patients being admitted to district general hospitals.

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Patients and methods

During 1973 and 1974, 34 doctors in 13 hospitals throughout Wales entered patients into this multicentre trial. Patients eligible for the trial were those aged under 70 years admitted to hospital within 48 hours of the onset of cardiac pain and who fulfilled at least two of three defined criteria for acute myocardial infarction: (i) typical clinical history, (ii) electrocardiographic changes of very probable acute myocardial infarct (World Health Organization 1959), and (iii) serum levels of cardiac enzymes (total creatine kinase or aspartate aminotransferase) more than twice normal for the laboratory in question. On the fifth day (day 5) after clinical onset of the infarct (defined as day 0), patients were allocated to be mobilised on day 5 or day 10 according to a randomised sequence of cards provided for each doctor. Patients considered on day 5 to have 'complicated' infarcts were excluded before randomisation at each doctor's discretion: 'complications' listed in the guidelines of the trial procedure included thromboembolic complications or the persistence of heart failure, hypotension, arrhythmias, or cardiac pain. The details of mobilisation day by day were not stipulated and total duration of stay in hospital was not controlled, though guidelines on both these points were given in the procedure. 'Mobilisation' meant sitting out of bed for two half-hour periods on the first day, with subsequently increasing activity until after one week they were out of bed for two hours a day and walking on the level. It was suggested that patients be discharged from hospital about a week after mobilisation.

Clinical details for each potentially eligible patient were recorded on day 0 and for trial patients also on day 5 and 10. Reasons for exclusion on day 5 were noted.

Follow-up details were obtained at out-patient attendances up to four years after the myocardial infarct in question, as a consequence of inadvertent delays in obtaining data at 12 months as planned. When all attempts at out-patient follow-ups failed (because of non-compliance, migration, or return home after holiday) follow-up information was next sought from the patient's general practitioner. This left 62 (8%) of the 746 original trial entrants for whom final tracings had to be sought from the National Health Service central register. Registrations with family practitioner committees provided evidence that 50 of these 62 patients remained alive, eight had died, and four remained untraced. These four patients have been excluded from the trial and from all calculations. The trial is therefore concerned with a total of 742 trial entrants. Mortality for the two groups was calculated using life table survivorship to three years and was compared by Mantel Haenzel test. Other comparisons were by χ^2 for non-parametric statistics (numbers with arrhythmia, dyspnoea, etc.) and by t test for parametric distributions (heart rate, blood pressure).

Results

Table 1 shows age and sex distribution of the 1035 patients, of whom 293 (28%) were excluded from entry into the trial on day 5 because of complications and 742 (72%) were entered into the trial on day 5. The characteristics of the early and the late mobilisation groups and of the group excluded from the trial are compared in Tables 1 to 4. Table 3 shows the interval between onset of cardiac pain and admission: in all groups about half the patients were admitted within four hours of the onset of cardiac pain and nearly a third within two hours. Patients excluded from the trial included a higher proportion with a past history of hypertension (Table 2) and with arrhythmias, severe cardiac pain, severe dyspnoea, bradycardia (<60/min), tachycardia (>120/min), or hypotension (systolic pressure <120 mmHg) on admission; a higher proportion showed electrocardiographic evidence of 'very probable infarct' and raised cardiac enzymes (Table 4).

Table 1 *Age and sex of patients*

Age	*Mobilised on day 5*		*Mobilised on day 10*		*Unfit on day 5 (excluded from trial)*	
	M	*F*	*M*	*F*	*M*	*F*
–34	4	0	4	0	0	0
35–44	30	4	34	2	16	2
45–54	107	9	109	12	69	10
55–64	123	25	130	26	125	19
65–69	36	9	54	24	38	14
Total	300	47	331	64	248	45

No significant differences.

Table 2 *Past history: numbers of patients (percentages in brackets)*

	Mobilised on day 5 n = 347	*Mobilised on day 10 n = 395*	*Unfit on day 5 n = 293*
Myocardial infarct	10 (3)	8 (2)	15 (5)
Angina	89 (26)	126 (32)	94 (32)
Hypertension	28 (8)	54 (14)*	51 (17)**
Diabetes	5 (1)	13 (3)	10 (3)

*Significant difference at $P < 0\cdot05$ (comparing day 5 mobilisation with day 10 mobilisation).
**Significant difference at $P < 0\cdot01$ (comparing unfit on day 5 with trial entrants).

Of the 742 patients entered into the trial, 347 (47%) patients were mobilised on day 5 and 395 (53%) on day 10. The two groups were shown to be well matched for sex and age (Table 1), past history of myocardial infarct, angina and diabetes (Table 2), and arrhythmia, severity of cardiac pain and dyspnoea, and recorded blood pressure, both on admission (Table 4) and on day 5. The only differences identified were a higher proportion of patients with known hypertension in the late mobilisation group (Table 2), and a higher mean heart rate on admission in the early mobilisation group (Table 4). There were no significant differences between the groups in numbers of patients being given oxygen, anticoagulants, antiarrhythmics, diuretics, or analgesics, either on admission or on day 5.

Survival curves for the first year for the 742 patients, calculated from the moment of randomisation on day 5, are shown in the Figure. There are no

Table 3 *Interval between onset of cardiac pain and admission to hospital (percentages in brackets)*

Interval (h)	*Mobilised on day 5*	*Mobilised on day 10*	*Unfit on day 5*
–2	101 (29)	119 (30)	87 (30)
3– 4	71 (20)	85 (22)	58 (20)
5– 8	65 (19)	76 (19)	46 (16)
9–12	39 (11)	44 (11)	38 (13)
13–24	39 (11)	32 (8)	23 (8)
25–48	22 (6)	22 (6)	24 (8)
Not recorded	10 (3)	17 (4)	17 (6)
Total	347	395	293

No significant differences.

Table 4 *Clinical findings on admission*

	Mobilised on day 5 *n*=347	*Mobilised on day 10* *n*=395	*Unfit on day 5* *n*=293
	Numbers (percentages in brackets)		
Electrocardiogram shows very probable infarct	208 (61)	244 (62)	216 (74)***
Enzymes (over twice normal)	266 (79)	304 (81)	252 (91)***
Arrhythmia	55 (16)	82 (21)	100 (35)***
Severe cardiac pain	47 (14)	70 (18)	65 (22)*
Severe dyspnoea	15 (4)	13 (3)	26 (9)**
	Mean ± standard deviation		
Heart rate	87 ±20†††	83 ±18	86 ±25
Systolic blood pressure	149 ±29	149 ±28	144 ±31*

* Significant differences at $P<0{\cdot}05$,** $P<0{\cdot}01$, and *** at $P<0{\cdot}001$ comparing unfit on day 5 with trial entrants.
†††Significant difference at $P<0{\cdot}001$ comparing day 5 mobilisation with day 10 mobilisation.

Table 5 *Time of follow-up assessment: months after entry to trial*

Months	*Mobilised on day 5* *Number (percentage)*	*Mobilised on day 10* *Number (percentage)*
8	3 (1)	4 (1)
9	9 (3)	6 (2)
10	9 (3)	8 (3)
11	26 (10)	31 (10)
12	85 (32)	93 (30)
13	32 (12)	21 (7)
14	14 (5)	28 (9)
15	13 (5)	7 (2)
16	5 (2)	7 (2)
17	3 (1)	7 (2)
18	3 (1)	12 (4)
19–24	11 (4)	22 (7)
25–30	15 (6)	25 (8)
31–36	21 (8)	20 (6)
37+	16 (6)	25 (8)
Total	265	316

significant differences in survival at one year between those mobilised on day 5 (41 deaths) and those mobilised on day 10 (42 deaths), and no significant difference for any month during the first year. The data in respect of mortality are complete for these 742 trial entrants (the four patients remaining untraced having been excluded from further consideration, see Methods). Data for survival beyond one year is also available but for diminishing numbers (51% of the 742 trial entrants at 13 months, 24% at 24 months, and 9% at 36 months). These data suggest a possible trend towards better survival during the second and third years in the day 10 mobilisation group (eight deaths) than in the day 5 group (15 deaths, $P<0{\cdot}05$) (see inset to Figure).

Morbidity was also assessed. Full clinical follow-ups were completed for 581 patients (90% of surviving trial entrants). It had been the intention that follow-up should be at 12 months after entry into the trial. Approximately half the patients were seen during 11th, 12th, or 13th months but inadvertently many were not followed up until later, the median follow-up assessment being 13 months in both groups (Table 5). At follow-up assessment there was no difference between the trial groups in the number of non-fatal reinfarctions that had occurred (20 in the day 5 mobilisation group and 19 in the day 10 group), nor in the features listed in Table 6.

Mortality was similarly analysed for subgroups of trial entrants identified by possible 'risk features'

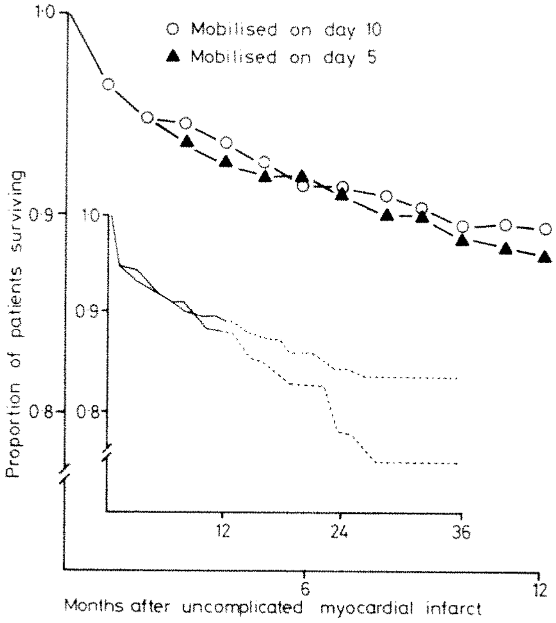

Fig. *Patient survival after uncomplicated myocardial infarct.*

Table 6 *Follow-up assessment*

	Mobilised on day 5 *n*=265	*Mobilised on day 10* *n*=316
	Number (percentage in brackets)	
Confined to bed	10 (4)	16 (5)
Not physically active	29 (11)	43 (14)
Angina at rest or limiting normal activity	15 (6)	15 (5)
Angina on mild or severe exertion	92 (35)	103 (33)
Dyspnoea at rest or limiting normal activity	13 (5)	15 (5)
Dyspnoea on mild or severe exertion	104 (40)	123 (39)
Arrhythmia	9 (3)	18 (6)
	Mean ± standard deviation	
Heart rate	80 ±12	79 ±11
Systolic blood pressure	145 ±22	144 ±25

No significant differences.

Table 7 *Survival of patients with potential 'risk features': life table survival at 12 months (numbers died in brackets)*

Potential 'risk feature' on admission	*Mobilised on day 5*	*Mobilised on day 10*	*Mobilised on day 5 or on day 10*
History of hypertension	0·63 (10)***	0·83 (9)	0·76 (19)***
Arrhythmia	0·78 (12)*	0·92 (6)	0·87 (18)
Severe cardiac pain	0·89 (5)	0·81 (12)*	0·85 (17)
Severe dyspnoea	0·73 (4)**	0·69 (4)**	0·71 (8)**
Bradycardia (HR < 60)	0·81 (3)	0·97 (1)	0·92 (4)
Tachycardia (HR > 120)	0·67 (8)***	0·64 (5)**	0·66 (13)***
Systolic BP < 120	0·86 (6)	0·83 (10)	0·85 (16)
Systolic BP > 180	0·88 (6)	0·83 (10)	0·85 (16)
All patients admitted to trial	0·88 (41)	0·89 (42)	0·89 (83)

*Significant differences at $P < 0{\cdot}05$, **at $P < 0{\cdot}01$, and ***$P < 0{\cdot}001$ comparing survival of patients with 'risk features' with survival of all patients admitted to the trial.

(Table 7). Patients with a previous history of hypertension, or with tachycardia or severe dyspnoea on admission experienced significantly poorer survival at one year. Arrhythmia or severe cardiac pain on admission showed possibly poorer survival.

Average stay in hospital was 13 days for the early mobilisation group and 16 days for the late mobilisation group. Early mobilisation in practice thus led to earlier discharge and resulted in lower costs to the National Health Service.

Discussion

The early mobilisation and the late mobilisation groups were comparable with respect to age, sex, previous history, interval between onset of cardiac pain and admission to hospital, clinical findings on admission, and treatment. Known hypertension was commoner in the late mobilisation group, but mean heart rate on admission was higher in the early mobilisation group, these two 'risk features' possibly balancing each other out with respect to first year mortality (Table 7). No obvious evidence of 'rule-breaking' was found to account for the slight excess of patients in the day 10 group. The trial shows no significant difference in the first year mortality, nor in morbidity assessed after a median period of 13 months. The largest similar trial previously carried out compared mobilisation after seven days and 14 days and also showed no disadvantage of early mobilisation (Royal Infirmary, Glasgow, 1973). More recently Abraham and colleagues showed fewer late non-fatal complications among 64 patients mobilised on day 6 compared with 65 on day 13, followed up for less than a year (Abraham *et al.*, 1975). In the only previous trial comparing earlier mobilisation a total of 189 patients were followed up for only six weeks (Hayes *et al.*, 1974). The present relatively large multicentre trial adds considerable support to the idea that mobilisation as early as day 5 is not detrimental.

Follow-up of trial patients after one year, albeit with reducing numbers, showed an unexpected trend towards lower mortality in the late mobilisation group. There appears to have been no obvious bias towards day 5 or day 10 mobilisation groups among those patients included in this late follow-up, nor any recognised difference between the representatives of day 5 and day 10 mobilisation groups with respect to the 'risk features' as listed in Table 7. Though the early mobilisation group as a whole had a higher mean heart rate on admission, a mismatch in respect of this 'risk feature' does not readily explain the widening difference in survival curves seen only after the first year of follow-up, and it was further shown that the deaths after the first year were not in fact associated with any of the identified 'risk features'. The trend towards a lower late mortality in the day 10 group remains unexplained.

This trial was carried out in district general hospitals throughout the region, in contrast to previous more centralised mobilisation trials. The conclusion that there is no significant difference in first year mortality or in morbidity after a median period of 13 months appears therefore to be of general application to all hospitals and has financial implications about costs borne by the National Health Service for patients admitted to hospital with uncomplicated acute myocardial infarction.

We are grateful to Professor A. L. Cochrane, Professor J. R. Muir, and the Working Party in Cardiology of the Welsh Hospital Board for initiating the study. We are greatly indebted to the many doctors, nurses, secretaries, and records staff who collaborated (a list of participating physicians is given below.)[1] Most of all we thank Mrs Elaine

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[1] The following consultants collaborated in this Welsh multicentre trial:
Professor A. W. Asscher, Cardiff; Dr P. Beck, Cardiff; Dr A. G. Chappell, Bridgend; Dr G. A. Coles, Cardiff; Dr E. A. Danino, Swansea; Dr L. A. G. Davidson, Cardiff; Dr F. L. Dyson, Neath; Dr R. B. Evans, Cardiff; Dr O. P. Galpin, Llandudno; Dr R. Greenwood, Cardiff; Dr J. N. Harris Jones, Swansea; Dr I. M. Hayes, Cardiff; Dr. A. H. Henderson, Cardiff; Dr N. Hodges, Bangor; Dr S. T. H. Jenkins, Aberystwyth; Dr J. H. Jones, Cardiff; Dr G. S. Kilpatrick, Cardiff; Dr D. G. Lewin, Caerphilly; Dr G. H. T. Lloyd, Rhyl; Dr O. Lloyd, Neath; Professor R. H. Mahler, Cardiff; Dr O. K. Makinson, Bangor; Dr. R. T. Maxwell, Bangor; Dr D. E. Meredith, Rhyl; Dr J. M. Morris, Bridgend; Professor J. R. Muir, Cardiff; Dr N. Oliver, Pontypridd; Dr. W. Phillips, Cardiff; Dr. J. Rhodes, Cardiff; Dr P. M. Smith, Cardiff; Dr J. de Sweit, Pontypridd; Dr A. J. Thomas, Cardiff; Dr J. P. Thomas, Cardiff; Dr F. K. Wright, Rhyl.

Elkington who co-ordinated all data collection throughout the trial and follow-up.

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Effect of coronary care on myocardial infarct mortality

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SUMMARY To study the effect of coronary care on the hospital mortality rate of acute myocardial infarction, patients treated in a coronary care unit (CCU) were compared with patients treated in general wards. To assess the comparability of cases, the coronary prognostic index of Chapman and Gray (1973) was modified. The modified index was based on serum aspartic aminotransferase (AST) level and cardiogenic shock. Modification was necessary because oliguria, the third variable on which the original index was based, could not always be determined for general ward cases. This modified index assessed very accurately the prognosis of myocardial infarct patients treated in hospital. Patients treated in the coronary care unit had a significantly higher mean modified prognostic index than control patients treated in the general wards, either before or after the introduction of coronary care. They also had a significantly shorter mean delay in admission than either group of general ward cases. These differences would be expected to worsen, not improve, the results of coronary care. By contrast, the two groups of general ward patients were very similar, as shown by mean modified prognostic index, mean admission delay, and results of correlation and regression analysis. In spite of their higher mean modified prognostic index and shorter mean admission delay, the coronary care unit patients had a significant reduction in their mortality rate, which dated from the opening of the unit, to little more than half that for the general ward patients. For general ward patients treated after the introduction of coronary care, on the other hand, the mortality rate was not significantly different from that for ones treated before. Furthermore, the reduction in mortality for coronary care unit cases was approximately the same over the whole range of infarct severity, and did not vary significantly from 15 per cent as the modified index rose from minimum to maximum values. It is suggested that severity of infarction should no longer be a reason for excluding any patients from coronary care.

Controversy continues about the effectiveness of coronary care (Donaldson, 1978; Hill *et al.*, 1978). There is little published evidence that the mortality rate of acute myocardial infarction is lower for patients treated in a coronary care unit than for those treated elsewhere, in groups of patients shown otherwise to have a similar probability of dying (Lindholm *et al.*, 1976; Peterson, 1978). This is in spite of the fact that the earliest coronary care units were established over a decade and a half ago (Brown *et al.*, 1963; Day, 1963; Wilburne and Fields, 1963), and notwithstanding numerous reports on the subject. Furthermore, while it seems that most cardiologists believe that coronary care units do improve the overall prognosis of acute myocardial infarction, it is also commonly believed that any reduction in mortality is greatest in patients with mild or only moderately severe infarcts, but small or non-existent in those with very severe infarcts (Chapman, 1970). For this reason, and because of the scarcity of facilities and staff, it has even been suggested that intensive coronary care be reserved either chiefly (Sloman and Brown, 1970) or exclusively (Robinson, 1965; Wyman and Hammersmith, 1968) for patients with less severe infarcts, or that these be treated in separate units from severe cases (Flynn and Fox, 1967).

It will now be shown that, for groups of patients with myocardial infarcts of similar severity as determined by a modified version of the coronary prognostic index of Chapman and Gray (1973), the hospital mortality was significantly less in patients treated initially in a coronary care unit than for those treated throughout in general wards, either before or after the introduction of coronary care. It will also be shown that the magnitude of this mortality reduction was approximately the same

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for infarcts of all degrees of severity, and did not vary significantly from 15 per cent over the whole range of the prognostic indices.

Patients and methods

Patients studied and methods used have already been described in detail (Chapman, 1970, 1971a, b; Chapman and Gray, 1973). Criteria for diagnosing acute myocardial infarction included a consistent clinical setting with at least one of the following: pathological Q waves or loss of R wave progression in the V leads, with serial ST segment and T wave changes; a serum AST level above 40 Sigma-Frankel units/ml;* a serum LDH level above 550 Berger-Broida units/ml; positive necropsy findings. Cardiogenic shock was diagnosed if hypotension ($BP \leq 80$ mmHg) and cyanosis and coldness of the extremities persisted for more than half an hour after pain relief and oxygen administration. (Because on multiple regression analysis it was found to make a statistically significant independent contribution to mortality, oliguria was analysed separately from the syndrome so defined.) For the AST estimations, blood was taken at 24 hours from the time of onset of the symptoms of the episode responsible for admission. The admission delay was the time elapsing between the onset of symptoms and arrival at the place of initial coronary care, whether general ward or coronary care unit.

MODIFIED CORONARY PROGNOSTIC INDEX

Severity of infarction was assessed using a modified version of the coronary prognostic index previously described by Chapman and Gray (1973). To arrive at this original index, more than 150 factors had been examined, and those found to be associated with a statistically significant change in the mortality rate according to χ^2 tests were subjected to multiple regression analysis. These factors included personal characteristics and habits, past history, coexistent disease, details of the admission episode, cardiac and extracardiac complications, arrhythmias, conduction defects, clinical observations, electrocardiogram, chest *x*-ray, and biochemical and haematological investigations. Multiple regression analysis was used to quantify the contribution of each factor to the outcome. Weighted scores were derived from the regression coefficients of a final multiple regression equation containing the only three variables found to have a significant independent influence on mortality, and the coronary prognostic index was based on these. Computers were used for all these statistical procedures (Chapman and Gray, 1973). Modification of this index was necessary to allow the inclusion in the present study of an adequate sample of general ward cases, because urine volume was not recorded routinely in the general wards; oliguria was one of the prognostic factors included in the original form of the index.

The modified prognostic index was based on the remaining two of the three variables used in the original index, namely AST level and cardiogenic shock. For its construction, multiple regression analysis was carried out once more on the data for the 357 cases on which the original index was based, but now correlating the outcome with only these two variables. The multiple correlation coefficient was highly significant ($R = 0{\cdot}504, P \ll 0{\cdot}01$), as was the partial correlation coefficient for each of the variables (AST, $r = 0{\cdot}271$; shock, $r = 0{\cdot}395$; for each, $P < 0{\cdot}0002$).

The new prognostic scores were calculated from these partial correlation coefficients, as previously described (Chapman and Gray, 1973). They are shown in Table 1. After these scores were applied to the same 357 cases, there was found to be a highly significant linear correlation between mortality rate and modified prognostic index (Fig. 1) ($r = 0{\cdot}913$, $P < 0{\cdot}0002$). According to the coefficient of determination (r^2), 83·4 per cent of the variation in mortality rate was explained by variation in the modified prognostic index. The standard error of estimate was 8·1 per cent.

PATIENTS

To determine the effect of treatment in the coronary care unit on mortality rate, three groups of patients were studied and the modified prognostic index was used to assess their comparability according to severity of infarction, and hence probability of dying. Of these three groups, one was treated in the general wards before the introduction of coronary care and the remaining two groups after this, one initially in the coronary care unit and the other concurrently in the general wards. The patients treated before the introduction of intensive coronary care were discharged from hospital or died there in the two-year period between 1 July 1966 and 30 June 1968, while those treated subsequently were admitted during the 18-month period between the opening of the unit on 20 August 1968, and 19 February 1970. Patients discharged from or dying in the general wards during the seven-week interval between these two periods had a mortality rate of 33 per cent, virtually identical with the 32 per cent

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*The AST levels were measured in Sigma-Frankel units/ml. These units, rather than the now standard international units/l, are still given because there is no direct or constant conversion factor between the two measurements (J. E. Dickeson, 1975, personal communication).

Table 1 *Scores for modified coronary prognostic index*

Factor		*Score*
AST level*	⩽ 40	0
	41– 80	5
	81–120	11
	121–160	16
	161–200	22
	⩾201	27
Cardiogenic shock	Absent	0
	Present	40

* In Sigma-Frankel units/ml.

prevailing in the preceding 12 months (Chapman, 1970), and will not be considered further here. The coronary care unit cases analysed in order to construct the modified prognostic index were admitted during the first 21 months of the operation of the unit, whereas this study was concerned only with admissions during the first 18 months

Every patient admitted to the coronary care unit was recorded in a register, and studied prospectively (Chapman, 1970). Sixty-four per cent of these admissions proved to have acute myocardial infarction; the remainder are not considered further. Another register was kept of infarct patients treated in the general wards during the same period. Most of these were also studied prospectively, though some not notified at the time were subsequently obtained from the medical records, which were searched systematically. General ward patients treated before the introduction of coronary care were studied retrospectively from the medical records.

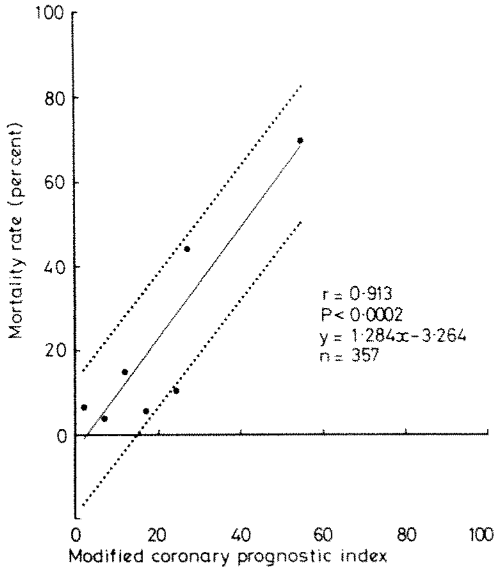

Fig. 1 *Coronary care unit cases, 20 August 1968 to 19 May 1970. In this Figure and subsequent Figures the dotted lines are drawn at twice the standard error of estimate from the calculated regression lines.*

ADMISSION POLICY

Although the original intention was to treat all cases of known or suspected acute myocardial infarction in the coronary care unit once this was operating, whether a patient was in fact admitted there or to a general ward depended principally on the availability of an empty bed in the unit at the time of admission. Patients with infarcts of any severity were accepted, and there was no age limit. However, it was realised that in some cases intensive coronary care would be inappropriate because of dementia, severe incurable coexistent disease, or old age associated with generally failing health. Nevertheless, some patients in these categories were admitted to the unit, and are included in its results. When there were more patients requiring admission than available beds in the unit, preference was given to those who were younger or otherwise healthier. If the episode of infarction was believed to have occurred more than 48 hours before presentation, a patient was usually not accepted for the coronary care unit unless there was a persistent conduction defect or other arrhythmia, but he might still be admitted to a general ward. Of the infarct patients who were already in the general wards, either because the diagnosis was not suspected on admission or because infarction occurred there (or in an operating theatre) during treatment of another complaint, some were treated in the wards, while others were transferred to the coronary care unit. The admission delay for the latter was still calculated from the time of arrival in the unit. Some patients with very severe infarcts whose treatment would have disturbed the calm of the coronary care unit were managed in a nearby intensive care unit, but still entirely by coronary care unit staff, both medical and nursing, according to the same principles of treatment. They, too, are included in the coronary care unit results.

For coronary care unit patients, admission as soon as possible after the onset of infarction was urged. Those referred from outside the hospital were admitted directly into the unit, not being reviewed in the casualty department unless priorities had to be established, while referrals from casualty itself or medical out-patients were also moved to the unit as soon as possible. Losing time to confirm the diagnosis of infarction, even by taking an electrocardiogram, was discouraged.

TREATMENT

Treatment was not uniform for patients in the general wards, either before or after the introduction of coronary care, and seldom included the use of antiarrhythmic agents or modern resuscitation, and never cardioversion or pacing. In the coronary care unit, by contrast, patients were managed strictly according to a procedure based on contemporary practice, with a specially trained team of doctors and nurses providing continuous cardiac monitoring and prompt treatment of conduction defects and other arrhythmias, myocardial failure, and cardiac arrest (Chapman, 1970, 1971a). There was an increasing tendency after the establishment of the coronary care unit for treatment in the general wards to resemble that given in the unit, and also for unit staff to be called for resuscitations, but with neither monitoring nor continuous observation little effective treatment of arrhythmias was possible.

ADDITIONAL NOTES ON STATISTICS

Some of the subgroups into which patients were divided according to their modified coronary prognostic index scores contained too few cases (15 or fewer) for percentage mortality rates to be calculated. As before (Chapman and Gray, 1973), these were combined into larger subgroups, but this did not significantly affect the mortality trends or results of regression analysis. Varying numbers in the subgroups meant that the subgroup intervals selected did not always correspond in the three groups of patients studied (from general wards before and after coronary care, and coronary care unit).

The significance of the correlation coefficients, and of the differences between means, independent constants, and regression coefficients was calculated using standard statistical tests, as described by Yeomans (1968).

The lower proportion of coronary care unit cases whose modified coronary prognostic index could be calculated, compared with general ward cases (307/432 vs. 414/476 and 157/193), had several possible explanations. Coronary care unit patients had an electrocardiogram taken more promptly after admission and of those who died more came to necropsy, so that relatively more of those dying less than 24 hours after the onset (at which peak AST level was estimated) may have had the diagnosis of infarction established by these other methods. Thus the proportion of infarcts in whom the diagnosis was proven may have been higher in the coronary care unit than in the general wards, without any corresponding increase in the number of cases whose modified prognostic index, needing an estimation of AST level, could be calculated. In the coronary care unit, also, the time at which blood was taken for the AST estimations was more accurately recorded, so that relatively more cases may have been rejected because of documented departures from the required 24-hour post-infarction timing of these (Chapman, 1971b; Chapman and Gray, 1973), which were not infrequent.

Nevertheless, the cases whose modified prognostic index could be calculated still constituted a representative sample of the whole group treated in the coronary care unit, as judged by the incidence of all other factors associated with a statistically significant change in mortality rate (B. L. Chapman, unpublished observations). Furthermore, their mortality rate of 16·3 per cent was not significantly different from the 19·2 per cent for the 125 patients whose modified prognostic index could not be calculated ($P > 0{\cdot}50$). The slightly lower mortality rate for those whose modified prognostic index could be calculated is explained by the fact that AST level does not reach its maximum until 24 hours after infarction, while the highest mortality rate occurs within that time (Chapman, 1970, 1971a, b; Chapman and Gray, 1973).

As established above, this modified coronary prognostic index forms a sufficient basis for comparing severity of infarction in patients treated in a coronary care unit. However, in such a unit the relation between admission delay and mortality rate is abolished, whereas elsewhere the sooner the patients are admitted after the onset of infarction the higher the mortality rate (Chapman, 1970, 1971a; Chapman and Gray, 1973; B. L. Chapman, unpublished observations). It was for this reason that the admission delays were also compared.

Results

The total numbers of cases of acute myocardial infarction treated in the general wards during the two years before the introduction of coronary care, and during the 18 months afterwards, and in the coronary care unit, were 476, 193, and 432, respectively. The mean times spent in hospital (±SD) were 22·4 (±13·8), 20·5 (±13·5), and 21·7 (±12·0) days, respectively. The differences between these means were not significant (general wards 1966 to 1968 vs. general wards 1968 to 1970, $P > 0{\cdot}05$; general wards 1966 to 1968 vs. CCU, $P > 0{\cdot}20$; general wards 1968 to 1970 vs. CCU, $P > 0{\cdot}10$). The respective hospital mortality rates were 34·7, 34·7, and 17·1 per cent.

ADMISSION DELAY

The mean admission delay for the 427 coronary care unit cases in which this was known was 13·6 (±15·9) hours, significantly less than the 16·3 (±19·6) hours for the 435 cases treated in the general wards before the start of coronary care, and the 17·2 (±20·8) hours for the 167 cases treated there subsequently (for each of the two pairs, P < 0·025). On the other hand, the small difference between the mean admission delays for the two groups of general ward patients was not significant (P > 0·30).

MODIFIED CORONARY PROGNOSTIC INDEX

The modified coronary prognostic index could be calculated for 414 of the patients treated in the general wards before the introduction of coronary care, 157 of those treated there subsequently, and 307 of those treated in the coronary care unit. The series studied therefore contained a total of 878 cases.

The mean modified prognostic index was higher for patients treated in the coronary care unit than for those treated in the general wards either before or after the introduction of coronary care (Table 2). These differences were highly significant, but, on the other hand, the difference between the means for the two groups of general ward patients was small and not significant (P > 0·30).

MORTALITY RATES

In spite of their significantly higher mean modified prognostic index, the coronary care unit patients had a mortality rate little more than half that of the general ward patients (Table 2). The differences in mortality were highly significant, whether the coronary care unit cases were compared with general ward cases treated before (P < 0·0005) or after (P < 0·005) the introduction of coronary care. By contrast, the mortality rates were practically the same for general ward patients treated before and after the establishment of the coronary care unit, and the difference was not significant (P > 0·60).

CORRELATIONS BETWEEN MORTALITY RATES AND MODIFIED PROGNOSTIC INDEX

In each of the three groups of patients studied, the mortality rate increased with increasing modified coronary prognostic index (Fig. 2, 3, 5). There was a very close linear correlation between mortality rate and modified prognostic index for patients treated in the general wards both before (r = 0·915, Fig. 2) and after (r = 0·889, Fig. 3) the introduction of coronary care, and for those treated in the coronary care unit (r = 0·927, Fig. 5). Each of these correlation coefficients was highly significant (P < 0·0002). The amount of the variation in mortality rate explained by variation in modified prognostic index was 83·8 and 79·0 per cent, respectively, for the general ward patients treated before and after the introduction of coronary care, and 86·0 per cent for the coronary care unit patients.

The rate at which mortality rate increased with increasing modified prognostic index was approximately the same in all three groups of patients. Thus the rate of increase, as measured by the regression coefficients, was 1·2 for both groups of general ward patients (Fig. 2, 3) and 1·3 for coronary care unit patients (Fig. 5). The differences between the regression coefficients were insignificant (for each of the three pairs, P > 0·95).

For the coronary care unit patients, there was no mortality additional to that described by the regression coefficient, and hence chiefly explained by variation in modified prognostic index (Fig. 5). The independent constant of the regression equation, in fact, had a small negative value (−3·5%). By contrast, the general ward patients had a large additional mortality of 15 per cent for those treated before the introduction of coronary care (Fig. 2) and 14 per cent for those treated subsequently (Fig. 3). The independent constant for each group of general ward cases (Fig. 2, 3) differed to a highly significant degree from the constant for the coronary care unit cases (Fig. 5) (for each of the two pairs,

Table 2 *Distribution of patients according to period and place of initial coronary care and to value of modified prognostic index, with associated mortality*

Period	*Place of initial coronary care*	*No. of cases*	*Modified coronary prognostic index**			*Mortality rate (%)*		
Before coronary care	General wards	414	13·0 ± 15·1	P > 0·30	P < 0·005	30·0	P > 0·60	P < 0·0005
After coronary care	General wards	157	12·3 ± 16·5	P < 0·01		28·0	P < 0·005	
	Coronary care unit	307	16·3 ± 17·7			16·3		
	Total	878						

*Mean ± SD.

$P < 0{\cdot}0002$). On the other hand, the independent constant for the general ward cases treated after the introduction of coronary care (Fig. 3) was not significantly different from the constant for those treated before (Fig. 2) ($P > 0{\cdot}10$). (These significance levels, of course, take into account the spread of the mortality rates above and below the regression lines. This scatter is expressed in the standard error of estimate, which was 7·5 and 8·9 per cent, respectively, for the general ward cases treated before and after establishment of the coronary care unit, and 7·4 per cent for the coronary unit cases.)

Because of their close similarity (according to mean admission delay, modified prognostic index, time in hospital, and mortality rate, as well as results of correlation and regression analysis), the two groups of general ward patients were combined (Fig. 4). For this composite group, the degree of linear correlation between mortality rate and modified prognostic index was higher than for either of the two constituent groups alone, and even higher than for the coronary care unit group, 88 per cent of the variation in mortality rate being explained by variation in modified prognostic index. The rate of change in mortality rate with modified prognostic index was 1·2 (Fig. 4), and the difference between the regression coefficients for the combined general ward patients (Fig. 4) and the coronary care unit patients (Fig. 5) was again insignificant ($P > 0{\cdot}95$). The mortality additional to that described by the regression coefficient was 15 per cent (Fig. 4), the difference between this independent constant for the combined general ward patients (Fig. 4) and that for the coronary care unit patients (Fig. 5) being highly significant ($P < 0{\cdot}0002$).

Discussion

The hospital mortality rate of acute myocardial infarction fell after the introduction of intensive coronary care, but only for those patients whose initial treatment was in the coronary care unit. For these, the mortality rate was little more than half that in patients treated throughout in general wards, either before or after the establishment of the coronary care unit.

The fall in mortality rate was associated with the beginning of the coronary care unit's operation. In the five years before the unit opened the rate had varied, though not significantly, between 32 and 39 per cent (Chapman, 1970). In the seven weeks before the unit opened, it had still been 33 per cent, virtually identical with the rate in the preceding 12 months. By contrast, the overall hospital mortality rate (for combined coronary care unit and general

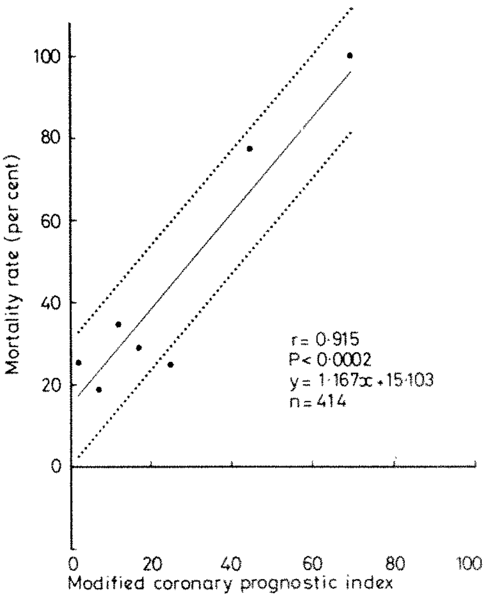

Fig. 2 *General ward cases, 1 July 1966 to 30 June 1968. Relation between mortality rate and modified coronary prognostic index.*

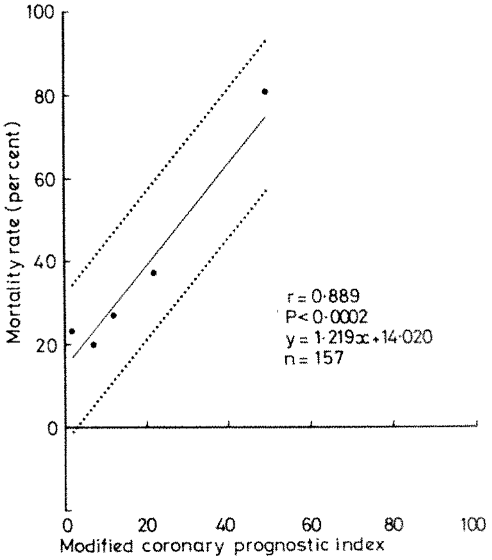

Fig. 3 *General ward cases, 20 August 1968 to 19 February 1970.*

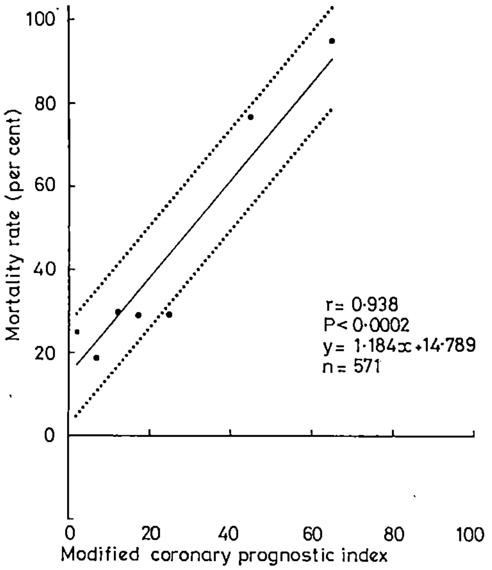

Fig. 4 *General ward cases, 1 July 1966 to 30 June 1968 combined with 20 August 1968 to 19 February 1970.*

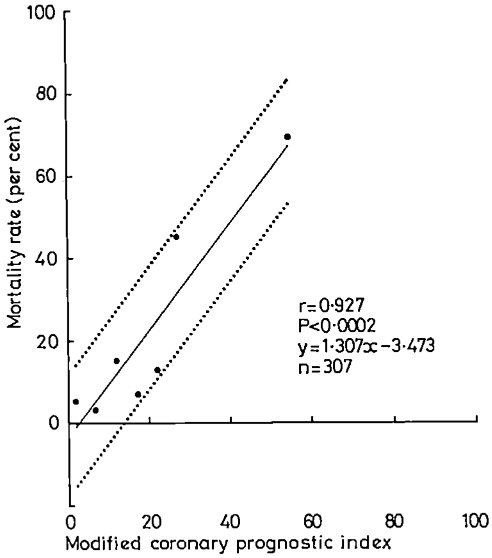

Fig. 5 *Coronary care unit cases, 20 August 1968 to 19 February 1970.*

ward patients) fell to only 23 per cent in the first 10 weeks of the unit's operation, and never varied significantly during the next two years (B. L. Chapman, unpublished observations).

This mortality reduction was in spite of the significantly shorter mean admission delay and significantly higher mean prognostic index of the coronary care unit cases. Such differences would tend to increase, not as actually happened, significantly reduce, the mortality rate of patients treated in the unit. On the other hand, for general ward patients the mortality remained practically the same after the unit's establishment as it had been before. Using the pre-CCU experience as the standard, this persistently high general ward mortality, unlike the coronary care unit mortality, was quite in keeping with the admission delay and modified prognostic index of the patients concerned.

For each of the three groups of patients studied, there was a close and statistically highly significant linear correlation between mortality rate and modified prognostic index. Between 79 and 88 per cent of the variation in mortality rate was explained by variation in modified index. This confirmed the usefulness of the index for determining the severity of infarction. The similarly high correlation coefficients for each of the three groups showed that this was independent of the place of initial coronary care.

The rate at which the mortality rate increased with increase in modified prognostic index was virtually the same for all three groups of patients. This rate of increase, as expressed by the regression coefficients, was 1·2 for both groups of general ward cases and 1·3 for the coronary care unit cases. Thus the regression lines were essentially parallel.

The reduction in mortality rate for patients treated in the coronary care unit was 15 per cent, and did not vary significantly over the whole range of the modified coronary prognostic index. Though the difference in mortality rate varied from 18 per cent at the lower end of the range of modified coronary prognostic index to 12 per cent at the upper end of the range, the difference between the slopes of the lines was still insignificant.

This finding that the mortality rate of all cases of acute myocardial infarction, regardless of severity, is reduced by 15 per cent means that severity of infarction should no longer be grounds for refusing admission to a coronary care unit. Admittedly, compared with the expected mortality rate of 15 per cent at the lower end of the range of modified prognostic index for patients treated in general wards, a 15 per cent reduction is a 100 per cent change, whereas compared with the expected rate of 82 per cent at the upper end of the range, a 15 per cent reduction is a change of only 18 per cent. Nevertheless, this still seems a worth-while reduction, and suggests that ideally coronary care should be available for all myocardial infarct patients.

The additional mortality, over and above that explained by variation in modified coronary prognostic index, reflecting severity of infarction, in general ward cases compared with coronary care unit cases, was presumably caused by untreated arrhythmias. It was pointed out previously that there are two components of the overall mortality of acute myocardial infarction treated outside coronary care units (Chapman, 1971b). The first component is directly related to the size of the infarct. The second component is unrelated to the severity of infarction. The higher mortality of such patients is generally believed to result from untreated arrhythmias (Adelson and Hoffman, 1961; Mower *et al.*, 1964; Lown *et al.*, 1967; Lawrie, 1969; Lovell and Prineas, 1971). It was also suggested previously that, in cases treated in a coronary care unit, the cardiac complications of acute myocardial infarction are not themselves the cause of the increased mortality associated with their presence, but are only indirectly related to the mortality rate, their occurrence merely reflecting the extent of infarction (Chapman, 1972; Chapman and Gray, 1973), to which the overall mortality rate itself is directly related (Chapman, 1971b). These complications included the arrhythmias (Chapman, 1972).

The present study had the advantage (Hill, 1955; Cochrane, 1972; Feinstein, 1973) of a concurrent control group. It also had the advantage of a retrospective control group, particularly since this was virtually identical with the concurrent group. The influence of varying diagnostic criteria on the selection of cases in different series has already been reviewed (Chapman and Gray, 1973). In the present series, the same criteria for the diagnosis of acute myocardial infarction were adhered to throughout. All clinical records and electrocardiograms were examined personally. It is often stated that hospital admission policies change over the years, so that groups of patients observed before and after the introduction of a new treatment may have different prognostic characteristics. In the present series, however, the general ward patients treated after the introduction of coronary care were very similar to those treated before. This was shown by similar admission delay, modified prognostic index, and time spent in hospital, as well as overall mortality rates, and results of linear correlation and regression analysis. For none of these was there any significant difference between the two groups. (The combining of the groups for joint comparison with the coronary care unit cases was justified by these similarities.)

However, there were differences attributable to changed admission policy for the coronary care unit cases. Their significantly shorter mean admission delay and higher mean modified prognostic index, compared with both groups of general ward patients, resulted respectively from the policy of admission soon after onset of symptoms, and the emphasis on coronary care for arrhythmias and complications, virtually all of which become more frequent as severity of infarction increases (Chapman, 1972; B. L. Chapman, unpublished observations). Thus, the policy of advising admission regardless of severity did not result in any lowering of the overall infarct severity of coronary care unit cases by diluting them with mild cases that would previously have been treated at home. In fact, just the opposite happened, and severity of infarction increased. However, it is possible that this increase was apparent only, and merely the result of improved observation and investigation in the coronary care unit (Oliver *et al.*, 1967).

The improved results were in no way attributable to a changed duration of observation. The distribution of patients according to their time spent in hospital was similar for all three groups studied. The mean for each group was about 21 days, much longer than is necessary to observe the period of maximum mortality, which is the first day or two after infarction (Chapman and Gray, 1973). The mean number of days from infarction to death for the general ward patients treated before the introduction of coronary care was 11 days, for those treated subsequently 10 days, and for those treated in the coronary care unit 9 days.

I am not aware of any other investigation into the effect of coronary care on myocardial infarct mortality conducted along the same lines as in the present study. However, its finding of a significant mortality reduction in coronary care unit cases is supported by published studies in which, according to a wide variety of different criteria, the severity of infarction in the coronary care unit cases was probably either equal to (Killip and Kimball, 1967; Parkinson *et al.*, 1967; Meltzer, 1968; Norris *et al.*, 1969; Bloomfield *et al.*, 1970; Hofvendahl, 1971; MacMillan and Brown, 1971) or greater than (Marshall *et al.*, 1968; Woodhouse and Hunter, 1968; Robinson, 1969; Chapman, 1970; Klaus *et al.*, 1970) that in the general ward case. This is in contradistinction to studies in which coronary care appeared to confer no benefit over general ward treatment (Linko *et al.*, 1970; Astvad *et al.*, 1974; Martin *et al.*, 1974; Colling *et al.*, 1976; Hill *et al.*, 1977). In three of these latter studies, however, patients were not treated in coronary care units at all, but in either intensive care units (Linko *et al.*, 1970; Martin *et al.*, 1974) or a busy general admission ward, where only two-thirds of patients could even be monitored (Astvad *et al.*, 1974). Thus only two reports presenting true coronary care unit results are at variance with the present study (Colling *et al.*, 1976; Hill *et al.*, 1977). In both these, however, the results were presented in the course of studies comparing hospital with home treatment, and will be referred to again later.

The uniform mortality reduction, in the present series, for infarcts of all degrees of severity as assessed with the modified prognostic index, is contrary to published opinion. It is usually stated that the greatest mortality reduction in acute myocardial infarction occurs with mild or only moderately severe infarcts, while there is little or no reduction with very severe infarcts. In only one previously published series was it claimed that the mortality reduction resulting from coronary care was uniform over any range of prognostic factors. Christiansen *et al.* (1971) stated that the reduction was 'constant for the sub-groups of age and sex'. However, the data presented did not fully support this claim, because though the mortality reduction was approximately the same for men and women, for the different age groups there was no consistent pattern.

The present results, of course, throw no light on the reported failure of coronary care to lower the mortality rate, as compared with treatment at home (Mather *et al.*, 1976; Colling *et al.*, 1976; Hill *et al.*, 1978). In the study of Mather *et al.* (1976) patients were allocated randomly to home or hospital for their initial coronary care. However, only 31 per cent of cases who were already a selected group (men aged under 70 years) were actually randomised. The mortality rate for their patients treated at home, while similar to that for those of Colling *et al.* (1976) and Hill *et al.* (1978), was less than for home-treated patients in the series of Fry and Dillane (1967) and Nichols (1968) and also, if all cases are considered, in that of Sleet (1968). Moreover, Armstrong *et al.* (1972) showed that, merely by varying the criteria for admission to the groups studied, the mortality rate for patients treated at home can be changed from below to considerably above that for coronary care unit patients. The present study clearly shows that, once patients are admitted to hospital, their mortality rate is significantly lowered when initial coronary care takes place in a coronary care unit.

Grateful acknowledgment is once again made of the contributions to the study of which this is a part by Dr J. M. Duggan, Dr J. T. Holland, Dr J. N. Walker, Mr H. M. Frith, Mrs J. Bubb, and many staff members of the Royal Newcastle Hospital, Newcastle Permanent Building Society Limited, CSIRO Division of Computing Research, West Middlesex Hospital (Isleworth), Hammersmith Hospital, and the Royal Society of Medicine (London). Mr C. H. Gray, Consultant Statistician at the CSIRO, once more generously gave statistical advice, and performed the multiple regression analysis.

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Angina in cold environment
Reactions to exercise

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SUMMARY Seventeen male patients with angina pectoris, and a history of increased severity of angina in the cold, performed submaximal bicycle exercise tests in a normal (20°C) and a cold environment (–10°C, 2·2 m/s wind velocity) wearing standardised clothing. Observations were made during and after serial short-term exercise periods each starting at 50 W, with continuous load increase of 10 to 30 W per minute, separated by 30-minute rest intervals.

In the group as a whole, maximal work load decreased by 7 per cent during exposure to cold. Heart rate, systolic blood pressure, and rate-pressure product were significantly higher during submaximal exercise in the cold, but at maximal work load there was no difference in heart rate, rate-pressure product, or magnitude of ST segment depression. The decrease in maximal work load exceeded 5 per cent (mean 11%) in 10 patients, who were described as cold-susceptible, while the decrease averaged 1 per cent in the seven non-susceptible patients. The cold-induced reduction in maximal work load showed a significant correlation with the increase in heart rate, blood pressure, and rate-pressure product during submaximal exercise.

After exercise, heart rate was significantly lower and blood pressure and rate-pressure product significantly higher in the cold than at normal temperature in all patients. In cold-susceptible patients, blood pressure was significantly higher at two and four minutes after exercise, and rate-pressure product at two minutes after exercise, than in non-susceptible patients, but in spite of this angina disappeared more quickly in cold-susceptible patients.

In conclusion, subjective cold intolerance was objectively demonstrated in 10 out of 17 patients with angina pectoris, by exercise in a room at –10°C. Susceptibility to cold was explained by a higher heart rate and blood pressure during exercise in the cold room, than during exercise in the room at normal temperature.

Patients with angina pectoris often experience a worsening of their symptoms in cold weather. The physiological explanation of this has been said to be the earlier appearance of myocardial oxygen deficit during exercise in the cold, which may be caused by increased work done by the heart (Epstein *et al.*, 1969), by nervous reflexes to the heart causing coronary vasoconstriction (Freedberg *et al.*, 1944; Mudge *et al.*, 1976), by release of sympatheticoadrenal hormones (Wilkerson *et al.*, 1974), or by cooling of the blood in the heart chambers and coronary arteries (Leon *et al.*, 1970).

However, not all patients with angina are susceptible to cold. The reason for this is not clear, but Neill *et al.* (1974), claimed that those patients with a low exercise tolerance are most affected, because of a relatively greater decrease in work performance. This conclusion was based on studies at rest, and there has been no study of the effects of cold on angina during exercise. We therefore studied the effects of exposure to cold on effort angina during standardised conditions, in order to see whether cold intolerance could be explained by changes which could be measured non-invasively.

Subjects

A questionnaire about the relation of their symptoms to cold was given to 50 consecutive patients with typical angina pectoris and electrocardiographic abnormalities during a routine bicycle ergometer test. All but two had observed worsening of

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symptoms at temperatures below 10°C. Seventeen of the patients with subjective cold intolerance (all men and all non-smokers, mean age 52 years, range 45 to 60 years) were invited to participate in the study and gave informed consent. The study was approved by the ethical committee of the hospital. All 17 patients gave a history of typical stable angina for at least 12 months. Six had had one or more myocardial infarctions and all had exercise-induced anginal pain and 0·2 to 0·6 mV horizontal or downward sloping ST depression on the electrocardiogram at the end of exercise. On a standardised stepwise ergometer test their work capacity, expressed as $W_{max\ 6\ min}$ (Strandell, 1964), was on average 105 W (range 70 to 150 W) and in all was limited by angina. None had hypertension, but one patient had signs of obstructive lung disease. Eight patients were taking beta-adrenergic receptor blocking agents in constant dosage. No other treatment except short-acting glyceryl trinitrate was allowed. Several patients had occasional unifocal ventricular premature beats at rest, without any increase during exercise.

Methods

ENVIRONMENT

Observations were made both in a cold environment in a special chamber and at normal room temperature. In the cold chamber the temperature of the air and walls was −10°C (SD ±0·4) and the relative humidity was 75 per cent; wind was directed toward the face and trunk at a velocity of 2·2 m/s (±0·1). Normal room temperature was set at 20°C (±1), with no wind and a relative humidity of 40 per cent (±8). Temperature was measured with thermocouples (copper/constantan) and the wind speed with a warm-wire anemometer. The calculated wind chill indices (Burton and Edholm, 1955) were 950 (cold) at −10°C, which causes an equivalent thermal wind decrement of about 18°C on unprotected skin (LeBlanc *et al.*, 1976), and 150 (normal) at 20°C. Clothing was carefully standardised. In the normal room the patients were dressed in short underwear, long summer trousers, shirt, socks, and ordinary shoes. In the cold chamber at −10°C a woollen cardigan, a pilot's summer overall, gloves, and a knitted woollen cap were added. The clothing was not windproof and the face and neck were uncovered.

To observe the changes in rectal and skin temperatures two patients exercised at 20°C and −10°C, with a 30-minute rest interval. The temperature was measured with thermocouples in the rectum 7 cm from the anus, and on 10 skin sites. Mean skin temperature was calculated by weighting the skin temperatures in the following manner: medial foot, 0·05; medial calf, 0·15; outer and inner thigh, back, chest, each 0·125; upper and lower arm, each 0·07; hand (thumb grip), 0·06; and forehead, 0·10. The rectal temperature increased slightly (0·1°C) after the first exercise period, and then remained unchanged, as was noted in an earlier investigation (Lassvik, 1978). Mean skin temperature decreased by 5·2±0·1°C at the end of exercise. The greatest local temperature changes were −18·0±0·7°C on the forehead, −6·0±1·1°C on the hand and foot, and −5·5±0·7°C on the chest. Both patients then exercised for a third time, one in the room at normal temperature and the other in the cold room, with resulting changes in body temperature identical with those observed in the corresponding earlier exercise period.

TEST PROCEDURE

The patients exercised in the cold chamber and in the room at normal temperature, with randomisation of the order of tests, the procedure being repeated on a second day with reversal of the test order. On each test day, the patients performed an initial 'trial' test at normal room temperature, so that each patient did three periods of exercise each day. As the 'trial' test was identical to the randomised test in the room at normal temperature, the occurrence of carry-over effects of exposure to cold on subsequent exercise at normal room temperature could be observed; no consistent carry-over effects were seen.

The exercise tests were performed on an electrically braked bicycle (Siemens-Elema 380) in which (according to the manufacturer) pedalling resistance did not change at low temperatures. The bicycle was not exposed to cold until immediately before the exercise and all electronic equipment was kept at normal room temperature. Sitting exercise was performed with an initial load of 50 W and thereafter a continuous load increase of 10 to 30 W per minute by use of a ramp generator (Lassvik, 1978). The rate at which load was increased was such that the patients experienced moderately severe angina, which was taken as the endpoint of the exercise period, after an exercise time of four to eight minutes. The patients rested sitting on the bicycle for five minutes before and after the exercise, but were then allowed to move around freely at normal room temperature between tests. The rest intervals between tests were 30 minutes. Each cold exposure lasted for 17±1 minutes.

A six lead praecordial electrocardiogram was recorded continuously at a paper speed of 10 mm/s with a forehead electrode as a reference (CH leads), and heart rate was calculated from the recordings.

Mean ST depression was measured at the appearance of angina and at maximal work load, at a paper speed of 50 mm/s, from five consecutive complexes in one of the leads CH 4-6. Systolic blood pressure was measured using a cuff on the upper arm and an ultrasound Doppler device, with the cuff and a flat probe beneath the clothing.

Heart rate and blood pressure were measured after five minutes of sitting on the bicycle before exercise, every minute during exercise, just before stopping exercise, and every minute for four minutes after exercise. The rate-pressure product (heart rate x systolic blood pressure) was calculated. Peak expiratory flow rate was measured 4·5 minutes after exercise, with a Wright peak flow meter. During exercise, the work load at appearance of pain and the maximal work load were noted. Measurements were also made at three minutes when most of the patients had no pain, and at approximately 4·5 minutes when all patients had angina. After exercise, the time for disappearance of angina was noted.

All tests were performed at the same time of day. Patients were not allowed to take food, nitrites, or muscular exercise for two hours before the tests. All patients had previously performed five serial exercise tests at normal temperature to establish reproducibility (Lassvik, 1978).

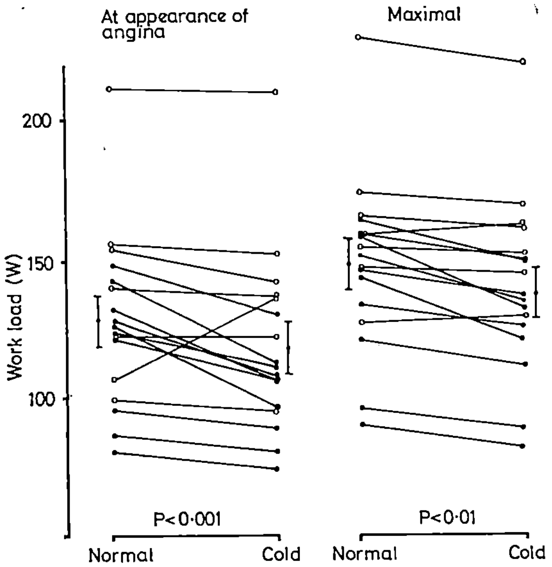

Fig. 1 *Angina and work performance in normal and cold environment.* ●, *cold-susceptible patients;* ○, *non-susceptible patients. Each symbol represents the mean of two exercise tests. Mean values ±SEM for all 17 patients are also shown.*

STATISTICS

For each patient the mean values were calculated for the two sets of randomised exercise periods and were evaluated with the t test for paired observations, and regression analysis. Multiple regression analysis was used for correlating cold-induced changes of exercise capacity with haemodynamic and clinical data (Draper and Smith, 1967). Patients in whom there was a more than 5 per cent decrease in maximal work load during exposure to cold were arbitrarily defined as cold-susceptible, and observations made in these patients were compared with those made in non-susceptible patients using the two-sample t test for unpaired data.

Results

The work load at appearance of pain decreased on exposure to cold by 8±1 per cent (mean±SEM) ($P<0{\cdot}001$), and the maximal work load by 7±1 per cent ($P<0{\cdot}01$) (Fig. 1). ST depression did not change between the normal and the cold

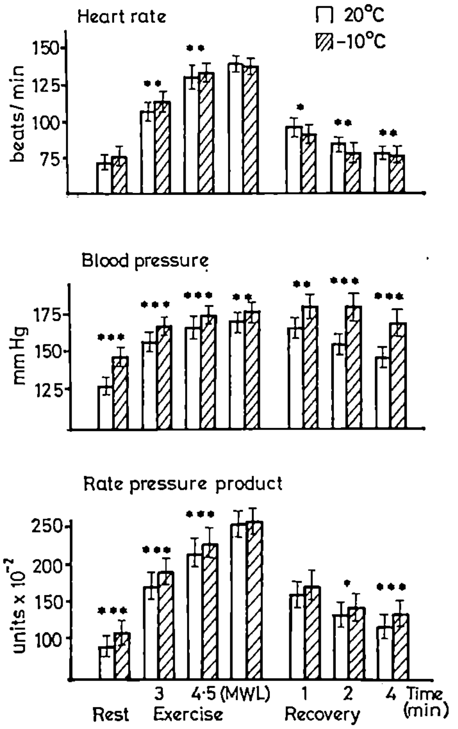

Fig. 2 *Heart rate, systolic blood pressure, and rate-pressure product in normal and cold environment before, during, and after exercise. Mean values ±SEM. Significance of differences:* $*P<0{\cdot}05$; $**P<0{\cdot}01$, $***P<0{\cdot}001$.

room (0·1 ± 0·02 mV at appearance of pain and 0·25 ± 0·04 mV at maximal work load, in both environments). Time for disappearance of angina did not change (122 ± 22s in normal and 111 ± 27s in cold room).

On exposure to cold, the heart rate was significantly higher during exercise (at three and at 4·5 minutes ($P < 0·01$) (Fig. 2), but in contrast the heart rate after exercise was significantly lower ($P < 0·01$) (Fig. 2). Blood pressure was significantly higher throughout exposure to cold ($P < 0·001$) (Fig. 2). During the first two minutes after exercise in the cold, blood pressure tended to be higher than at maximal work load. The greatest individual rise in blood pressure was 45 mmHg, from 180 mmHg at maximal work load to 225 mmHg two minutes after exercise. In contrast, at normal room temperature blood pressure decreased gradually and significantly from maximal work load to four minutes after exercise ($P < 0·01$) (Fig. 2). Rate-pressure product was significantly higher at cold exposure ($P < 0·001$) except at maximal work load and at one minute after exercise (Fig. 2).

The cold-induced decrease in maximal work load was significantly correlated with the cold-induced increase in heart rate and rate-pressure product after three minutes of exercise ($P < 0·001$ and $P < 0·01$, respectively) and with the increase in heart rate, blood pressure, and rate-pressure product after 4·5 minutes of exercise ($P < 0·001$, $P < 0·05$, and $P < 0·01$, respectively) (Fig. 3). No correlation was found between cold-induced decrease in maximal work load and changes in heart rate or rate-pressure product at rest or at maximal work load, or blood pressure changes at rest, at three minutes of exercise, or at maximal work load. Cold-induced changes in time for disappearance of angina were not correlated with changes in heart rate, blood pressure, or rate-pressure product after exercise.

Cold-induced changes in maximal work load were not related to the patient's age, height, weight, duration of angina, or number of infarctions, medical treatment, maximal work load, maximal work time, performed work, time of the year for the investigation, or a rough estimate of the patient's outdoor activities.

Peak expiratory flow rate after exercise was not significantly different in the cold room and in the room at normal temperature (503 ± 30 l/min and 501 ± 30 l/min, respectively).

Occasional ventricular premature beats were seen in seven patients both at rest and during exercise, with no increase on exposure to cold.

COLD-SUSCEPTIBLE VS NON-SUSCEPTIBLE PATIENTS

In 10 cold-susceptible patients the cold-induced reductions of work load at appearance of pain and maximal work load were 14 ± 2 per cent and 11 ± 1 per cent, respectively (both $P < 0·001$). Time for disappearance of angina decreased by 14 ± 6 per cent ($P < 0·05$). In seven non-susceptible patients, work load at appearance of pain and maximal work load did not change significantly (−1 ± 0%). The time for disappearance of angina increased, but the change was not significant (10 ± 9%). The differences between the groups were significant in respect not only of maximal work load but also work load at appearance of pain ($P < 0·001$) and time for disappearance of angina ($P < 0·05$). Five of the cold-susceptible patients and three of the non-susceptible patients were taking beta-adrenergic blocking drugs.

During exercise in the cold (at three and 4·5 minutes) cold-susceptible patients had significantly greater increases in heart rate ($P < 0·01$) and rate-pressure product ($P < 0·05$) than non-susceptible patients, averaging six beats/minute and 1400 units,

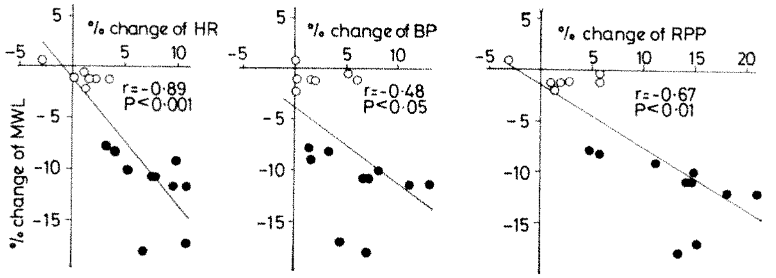

Fig. 3 *The correlation between percentage changes* of maximal work load (MWL) and heart rate (HR), systolic blood pressure (BP), and rate pressure product (RPP) after four and a half minutes of exercise in a cold room compared with room at normal temperature. *Percentage change calculated (e.g. for heart rate) as* $\frac{HR_{-10^\circ} - HR_{20^\circ}}{HR_{20^\circ}} \times 100$

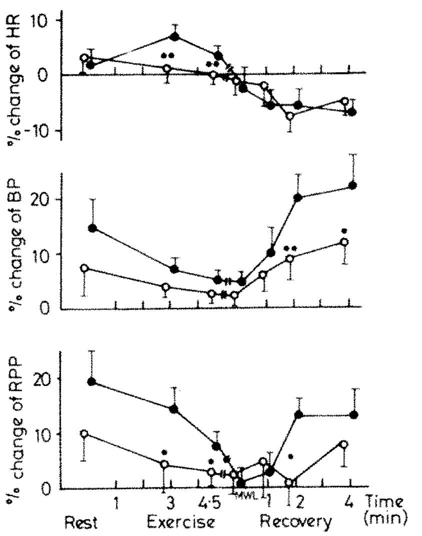

Fig. 4 *Percentage changes in heart rate (HR), blood pressure (BP), and rate-pressure product (RPP) in 10 cold-susceptible patients (●) and seven non-susceptible (○) patients, in cold room compared with room at normal temperature. Significance of differences: *P < 0·05, **P < 0·01.*

respectively (Fig. 4). Blood pressure tended to be higher in cold-susceptible patients (mean difference 6 mmHg) but the differences were not significant. After exercise, cold-susceptible patients had significantly greater increases in blood pressure at two minutes (P < 0·01) and four minutes (P < 0·05), and in rate-pressure product at two minutes (P ± 0·05) than non-susceptible patients during exposure to cold.

Discussion

Although all the patients investigated gave a history of reduced exercise tolerance in the cold, almost half the patients showed no decrease in working capacity on exposure to the cold (−10°C, 2 m/s wind velocity). As the exercise procedure included successive exercise periods on the same day, it was possible that the warming up effect of the first period of exercise, and carry-over effects of the cold exposure on the next exercise period, might decrease differences between tests. The design of the investigation however, excluded such effects (see also Lassvik, 1978). Another possibility is that the laboratory procedure failed to reproduce the real life situation which includes many uncontrolled circumstances. On the other hand, physical conditions, such as wind, rain, and snow, and psychological factors such as the expectation of untoward effects of cold in the real life situation, may make the laboratory experiment better for identifying the effects of cold exposure *per se*.

The levels of rate-pressure product at moderately severe angina were the same during exercise at normal temperature and in the cold chamber. This indicates that the constant relation between angina pectoris and rate-pressure product, reflecting myocardial oxygen demand (Robinson, 1967), still holds in a cold environment. The significant relation between cold-induced decrease of maximal work load and increases in heart rate, blood pressure, and rate-pressure product suggests that the observed reduction in maximal work load in cold-susceptible patients is probably the result of the increase in the work done by the heart.

We found a significantly greater increase in both heart rate and blood pressure in all patients during submaximal exercise in the cold chamber compared with the room at normal temperature. This suggests an increase in both cardiac output and peripheral resistance which has been shown to occur in healthy volunteers both during acute (Keatinge *et al.*, 1964) and long-term exposure to cold (Hanna *et al.*, 1975). In patients with angina pectoris, and in healthy controls, cold has been found to increase peripheral resistance and blood pressure at rest (Neill *et al.*, 1974). In addition, Epstein *et al.* (1969) found that during light exercise in the cold, peripheral resistance remains high. There is no increase in heart rate at rest, a finding which may be explained by the baroreceptor reflex reducing sympathetic cardio-acceleration (Sarnoff *et al.*, 1965). With local cooling of the face, heart rate may even decrease (Hayward *et al.*, 1976). During light exercise, baroreceptor reflex activity might likewise suppress cold-induced increase in heart rate as was seen in the study by Epstein *et al.* (1969). In our investigation the work load was greater and the environment considerably colder, probably resulting in increased sympathetic activity which could explain why the heart rate was higher during exercise in the cold chamber compared with the normal room temperature. The importance of heart rate for the development of ischaemia is shown by the favourable action of beta-adrenergic blocking agents in angina, and by atrial pacing studies.

Another observation in this study was that after exercise in the cold room, blood pressure did not fall normally but remained high, and in a few patients increased further. Heart rate fell more rapidly than at normal temperature, probably because of increased baroreceptor reflex activity resulting from the higher blood pressure. In spite of this, the rate-pressure product remained significantly higher in all patients. In cold-susceptible patients, cold-induced increases in both blood pressure and rate-pressure product after exercise were significantly greater than in non-susceptible patients, but nevertheless angina disappeared more rapidly. An explanation of the faster disappearance of angina after exercise in cold-susceptible patients might be that the higher arterial pressure improved coronary perfusion; also a faster fall in heart rate during the first minute after exercise might reduce oxygen demand and also improve myocardial oxygen supply because of a longer diastole. On the other hand, a practical implication of the high post-exercise blood pressure during exposure to cold might be a further decrease in the angina threshold during subsequent exercise.

The rapid decrease in heart rate and disappearance of angina after exercise during exposure to cold might indicate that the haemodynamic changes are caused by nervous reflexes rather than by circulating catecholamines. Strong baroreceptor reflex activity could, however, be concealing sustained catecholamine effects on heart rate. Keatinge *et al.* (1964) found that there was only a small increase in plasma adrenaline even during very intense acute skin cooling, and it seems likely that the haemodynamic changes induced by the short-term exposure to cold in this study are caused mainly by direct sympathetic nervous reflexes.

In conclusion, differences in the behaviour of heart rate and blood pressure could explain the different effects of cold on the development of angina during exercise and recovery after exercise in a group of patients with angina pectoris, and objectively identify a subgroup of cold-susceptible patients.

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Haemodynamic and electrocardiographic accompaniments of resting postprandial angina[1, 2]

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SUMMARY The early postprandial changes in 10 patients with angiographically proven coronary artery disease and history of postprandial angina were studied by the continuous recording on magnetic tape of the electrocardiogram and haemodynamic variables. The significant changes 20 minutes after a meal not followed by angina included increases in cardiac index and stroke index, with a decrease in systemic vascular resistance. When angina developed after a meal, there were significant increases in mean systemic arterial blood pressure, heart rate, pulmonary capillary wedge pressure, and systemic vascular resistance with decreases in stroke index at the onset of pain rather than at the onset of ischaemic electrocardiographic abnormalities. The first haemodynamic variable to change was pulmonary capillery wedge pressure which tended to increase coincident in time with the electrocardiographic abnormalities. In all cases, postprandial angina occurred within 25 minutes after a meal. In every instance, there was little or no change in the product of heart rate and systolic arterial blood pressure at the onset of the ischaemic electrocardiographic abnormalities at a time when the pulmonary capillary wedge pressure had begun to rise. Postprandial angina, like many cases of rest angina, may arise on the basis of a primary decrease in myocardial perfusion, the nature of which is unclear but merits further investigation.

Angina occurring at rest but after a meal, is a well-known phenomenon in patients with advanced coronary artery disease (Cohen *et al.*, 1966; Friedberg, 1966; Harrison and Reeves, 1968). It generally occurs within the first 20 minutes after eating (Lewis, 1931; Wayne and Graybiel, 1933; Goldstein *et al.*, 1971), though occasionally it has been known to develop up to three to five hours later especially after a large fatty meal (Kuo and Joyner, 1955; Regan *et al.*, 1961). Furthermore, postprandial exercise tolerance is much impaired in these patients though a clear explanation for the phenomenon is not available (Wayne and Graybiel, 1933; Berman *et al.*, 1950; Goldstein *et al.*, 1971). It has been felt by some that myocardial ischaemia under these circumstances may be produced by an increase in oxygen demand related to postprandial increases in cardiac work (Friedberg, 1966; Harrison and Reeves, 1968; Goldstein *et al.*, 1971; Vatner *et al.*, 1970). However, an alternative mechanism involving primary coronary vasoconstriction caused by a reflex arising in the digestive tract (Wayne and Graybiel, 1933; Gilbert *et al.*, 1940; Morrison and Swalm, 1940), with a reduction in coronary blood flow (Kuo and Joyner, 1955; Regan *et al.*, 1961) has also been considered of significance in the development of postprandial angina.

An analysis of the haemodynamic changes preceding the onset of the ischaemic electrocardiographic abnormalities has been thought to be a useful tool for the indirect evaluation of the mechanism of angina (Guazzi *et al.*, 1971; Maseri *et al.*, 1975) and in a few instances changes in myocardial oxygen demand preceding the onset of angina have been reported. However, such sequential haemodynamic studies on resting postprandial angina have not been reported. This study was therefore undertaken to define the mechanism of postprandial angina from the records of various haemodynamic variables and the electrocardiogram obtained during

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the continuous monitoring of these functions on magnetic tape.

Patients and methods

Ten patients, eight men and two women, age range 46 to 82 years, were included in this study. All had a history of resting postprandial angina at home and while in hospital. They had coronary artery disease as indicated by a greater than 70 per cent obstruction of at least two major vessels documented by coronary angiography (seven patients), or by history of a previous myocardial infarction (three patients). All of them also had a history of exertional angina. All patients gave the history of postprandial angina as occurring within 20 to 25 minutes after a meal; the pain did not last longer than five minutes and it was readily relieved either spontaneously or by glyceryl trinitrate (GTN). In each instance acute myocardial infarction was subsequently ruled out by serial electrocardiographic and enzyme criteria. Patients with clinical or radiological evidence of heart failure or shock were not studied. Previous therapy except for sublingual GTN was discontinued at least 12 hours before the study. In some cases propranolol was tapered over a 48-hour period.

After written informed consent was obtained, arterial and pulmonary artery catheters were inserted and baseline measurements made. Arterial pressures and a modified lead of the electrocardiogram were continuously monitored while being displayed on an oscilloscope and recorded on magnetic tape. Cardiac output measurements were performed every two hours, and immediately before and 20 minutes after each meal. When angina supervened, cardiac output was also measured at the onset of the pain before the administration of GTN (if this was given) and when it was relieved. After stabilisation, all the haemodynamic variables and the electrocardiogram were recorded in every patient for varying periods before at least one meal and continuously thereafter for periods ranging between eight and 33 hours, average 21 hours. The continuous recording of the heart rate, arterial blood pressure, and the electrocardiogram permitted the delineation of the precise time relation in the alterations in these variables. Since the cardiac output could not be measured continuously, the changes occurring in this variable could only be evaluated with reference either to the last recorded measurement (often two hours previously) or to the one determined after the complete relief of pain under stable conditions. Each meal consisted of a mixed diet with a caloric content not exceeding 500 calories. On several occasions, the patents were fed by a nurse to facilitate the recording of haemodynamic variables. The patients were instructed to push an alarm button at the very onset of pain and to inform one of the investigators of the time of onset and complete relief of pain. A 12 lead electrocardiogram was taken at the beginning of the study, during pain, and after its relief. The procedure was approved by the Human Subjects Committee of the Cedars-Sinai Medical Center.

Arterial blood pressure was measured through a 21-gauge 2-inch long cannula inserted percutaneously into the radial artery. Pulmonary artery, pulmonary capillary wedge, and right atrial pressure were measured through a no. 7 Fr Swan-Ganz catheter inserted by cutdown into the antecubital vein, or percutaneously into the internal jugular vein. Cardiac output was measured in triplicate by the thermodilution technique (Ganz and Swan, 1972), and the arterial and pulmonary artery catheters were attached to a Stratham P23DB pressure transducer and Hewlett-Packard pressure amplifiers. The pressures and a modified lead V5 of the electrocardiogram were continuously displayed on an oscilloscope and recorded in a VR-3300 Data Tape magnetic tape recorder (Consolidated Electrodynamics). Both catheters were filled with a heparinised 5 per cent dextrose in water and flushed at least once every hour. The zero level was measured at 5 cm below the angle of Louis. Pressure measurements were taken by averaging all values over two respiratory cycles. At the end of the study the data stored on the magnetic tapes were recorded on a six-channel Clevite Brush Mark 200 ink recorder, at various paper speeds for the analysis of the overall patterns of change, as well as the beat-to-beat alterations.

Results

CLINICAL DATA

The clinical details of patients with respect to the extent of coronary artery disease, previous history of myocardial infarction, and treatment before the initiation of the study are shown in Table 1. Of the 10 patients, six experienced postprandial angina during the study. In all of them pain was promptly relieved by glyceryl trinitrate. The appearance of angina was not related to the amount of food, and in every instance it occurred within the first 25 minutes after the end of the meal. One patient developed angina 10 minutes after having eaten an apple, and another 15 minutes after a half-cup of cottage cheese.

HAEMODYNAMICS

The values of the measured haemodynamic variables in eight patients immediately before, and 15 to 20 minutes after finishing a meal not followed by pain, are shown in Table 2a. The measurements taken before the meal, and at the onset of postprandial pain and when the pain was relieved, in the six patients who experienced angina during the study, are shown in Table 2b. The trend in the haemodynamic changes was consistent in each of the three patients (cases 1, 5, 9) in whom more than one complete set of measurements with an without pain were available. The postprandial haemodynamic changes in the absence of pain indicated a significant ($P < 0·01$) decrease in systemic vascular resistance associated with a significant increase in cardiac index ($P < 0·01$) and stroke index ($P < 0·05$) without consistent changes in the heart rate (Fig. 1). The arterial pressure tended to decrease and there were no appreciable changes in pulmonary arterial, pulmonary capillary wedge, or right atrial pressure. In one patient (case 11), the resting pulmonary capillary wedge was abnormally raised in the absence of clinical or radiological signs of heart failure. This patient had had three myocardial infarctions in the past. The postprandial haemodynamic change in this patient was suggestive of a relative improvement in left ventricular function as indicated by an increase in stroke index and a

Table 1 *Clinical features of patients studied*

Case no.	*Sex*	*Age (y)*	*History of myocardial infarction*	*Previous therapy*	*No. of vessels involved (angio)*
1	M	82	1	Propranolol 80 mg; nitrates	—
2	M	73	2	Propranolol 80 mg	—
3	F	71	—	Nitrates	3
4	M	60	—	—	3
5	M	62	—	Propranolol 40 mg; nitrates	3
6	F	52	1	Propranolol 240 mg; nitrates	—
7	M	69	—	Propranolol 80 mg; nitrates	3
8	M	46	1	Propranolol 240 mg; nitrates	2
9	M	62	—	Nitrates	2
10	M	65	3	Nitrates	3

Table 2a *Postprandial haemodynamic changes in patients with advanced coronary artery disease in absence of chest pain*

Case no.	*HR (beats/min)*	*Systemic arterial pressure (S/D) (mmHg)*	*$\overline{AP}$ (mmHg)*	*Systemic arterial pressure × HR × 0·001*	*PA pressure (S/D) (mmHg)*	*PCWP (mmHg)*	*RAP (mmHg)*	*CI (l/min per m^2)*	*SI (ml/beat per m^2)*	*SWI (gm/beat per m^2)*	*SVR (dynes/s per cm^{-5})*
1 B	72	135/52	80	9·7	16/6	5	4	1·95	27·1	27·6	1888
A	80	110/45	67	8·8	12/4	4	4	2·15	26·9	23·0	1420
2 B	58	142/54	83	8·2	32/12	13	5	2·06	35·5	33·8	1793
A	68	130/48	75	8·8	37/14	14	5	2·24	32·9	27·3	1478
4 B	81	130/66	87	10·5	20/7	7	5	2·87	35·4	38·5	1299
A	75	130/60	83	9·8	18/8	7	6	3·02	403	41·7	1164
5 B	68	135/65	88	9·2	32/13	12	6	2·77	40·7	42·1	1250
A	64	138/66	90	8·8	34/14	11	6	3·11	48·6	52·2	1152
6 B	82	130/65	87	10·7	22/10	9	3	2·10	25·6	27·2	1926
A	83	109/58	75	9·0	22/10	10	3	2·30	27·7	24·5	1512
8 B	62	103/56	72	6·4	21/7	6	5	2·00	32·3	29·0	1279
A	67	104/54	71	7·0	23/6	5	3	2·90	43·3	38·9	892
9 B	55	127/60	82	7·0	20/8	8	5	2·12	38·5	38·7	1630
A	53	132/60	88	7·0	23/9	9	6	2·17	40·9	43·9	1699
10 B	90	125/90	102	11·3	43/24	23	10	2·47	27·4	29·4	1716
A	90	120/85	97	10·8	43/23	20	10	3·17	35·2	36·9	1256
B	71·0 ±4·4	128·4 ±4·1/ 63·5 ±4·2	85·1 ±3·0	9·1 ±0·6	25·8 ±3·2/ 10·9 ±2·1	10·4 ±2·1	5·4 ±0·7	2·29 ±0·13	32·8 ±2·0	33·3 ±2·1	1598 ±100
M ± SEM											
A	72·5 ±4·2	121·6 ±4·5/ 60·3 ±4·4	80·8 ±3·7	8·8 ±0·5	26·5 ±3·7/ 11·0 ±2·1	10·0 ±1·8	5·4 ±0·8	2·63 ±0·16‡	37·0 ±2·7†	36·1 ±3·6	1322 ±90*

A, before meal; B, after meal; HR, heart rate; $\overline{AP}$, mean arterial pressure; S/D, systolic/diastolic; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; CI, cardiac index; SI, stroke index; SWI, stroke work index; SVR, systemic vascular resistance. *$P < 0·01$; †$P < 0·05$; ‡$P < 0·02$.

Table 2b *Haemodynamic changes during postprandial angina*

Case no.	*HR (beats/min)*	*Systemic arterial pressure (S/D) (mmHg)*	$\overline{AP}$ *(mmHg)*	*Systemic arterial pressure × HR × 0·001*	*PA pressure (S/D) (mmHg)*	*PCWP (mmHg)*	*RAP (mmHg)*	*CI (l/min per m²)*	*SI (ml/beat per m²)*	*SWI (g m/beat per m²)*	*SVR (dynes/s per cm⁻⁵)*
1 B	68	168/74	105	11·4	26/11	11	5	2·20	32·4	41·4	2204
CP	87	184/86	119	16·0	52/26	25	6	2·15	24·7	31·0	2554
R	81	164/70	101	13·3	32/14	12	5	2·22	27·4	38·4	2180
2 B	62	155/54	88	9·6	40/15	15	5	2·07	33·4	33·2	1897
CP	120	192/89	123	23·0	70/36	38	11	2·22	18·5	20·9	2347
R	64	132/45	74	8·4	28/10	12	2	2·07	32·3	27·2	1646
3 B	92	174/58	97	16·0	36/16	8	6	2·85	31·0	37·5	1462
CP	105	240/120	160	25·7	52/34	32	12	—	—	—	—
R	94	180/64	103	16·9	30/11	10	5	—	—	—	—
4 B	66	135/70	92	8·9	24/9	7	5	2·62	39·7	45·9	1555
CP	98	150/90	110	14·7	54/30	28	6	2·41	24·5	27·3	2180
R	70	160/90	113	11·2	28/13	10	5	2·61	37·3	52·2	1982
5 B	72	115/58	77	8·3	36/13	12	7	2·87	39·9	35·3	1016
CP	92	160/84	109	14·7	54/34	28	10	2·89	31·4	34·6	1485
R	79	153/80	104	12·1	22/10	8	6	2·44	30·9	40·3	1508
7 B	83	135/67	90	11·2	24/10	8	4	2·23	26·9	30·0	1719
CP	87	150/70	97	13·0	30/16	14	6	2·40	27·6	31·2	1733
R	84	125/66	86	10·5	20/10	7	4	2·00	23·8	25·6	1829
B	73·8 ±4·7	147·0 ±9·2/ 63·5 ±3·2	91·5 ±3·8	10·9 ±1·1	31·0 ±2·9/ 12·3 ±1·1	10·2 ±1·2	5·3 ±0·4	2·47 ±0·14	33·9 ±2·1	37·2 ±2·9	1642 ±165
CP	98·2 ±5·2†	179·3 ±14·1‡/ 89·8 ±6·7†	119·7 ±8·9‡	17·9 ±2·1*	52·0 ±5·2**/ 29·3 ±3·0¶	27·5 ±3·3§	8·5 ±1·1‡	2·41 ±0·13	25·3 ±2·1†	29·0 ±2·3	2059 ±197†
R	78·7 ±4·3	152·3 ±8·4/ 69·2 ±6·3	96·8 ±5·8	12·1 ±1·2†	26·6 ±1·9§/ 11·3 ±0·7§	9·8 ±1·0¶	4·5 ±0·6†	2·27 ±0·11	30·3 ±2·3	36·7 ±4·8	1829 ±119

B, before meal; CP, during chest pain; R, during relief; † P < 0·05; ‡ P < 0·02; * P < 0·01; ** P < 0·005; § P < 0·002; ¶ P < 0·001. Further abbreviations see Table 2a.

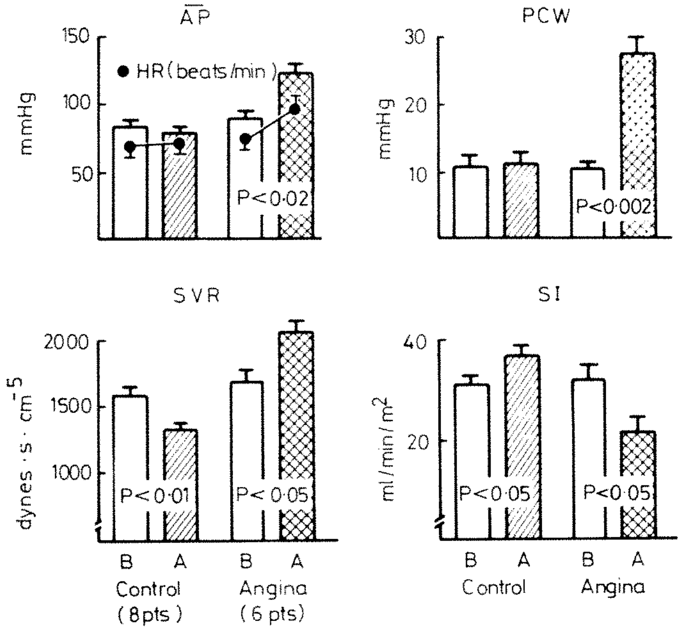

Fig. 1 *Mean postprandial haemodynamic changes with and without the occurrence of angina in patients with ischaemic heart disease.* $\overline{AP}$*, mean arterial pressure; PCW, mean capillary wedge pressure; SVR, systemic vascular resistance; and SI, stroke volume index. In each panel* B *represents mean values before the ingestion of a meal and* A *represents figures for the corresponding variables after a meal. Note that in the absence of angina, SVR falls and SI increases significantly with no change in PCW. During episodes of angina postprandially, there are significant increases in SVR and PCW,* $\overline{AP}$ *associated with a fall in SI.*

moderate decrease in pulmonary capillary wedge.

When postprandial angina occurred, however, there was a uniform increase in pulmonary arterial, pulmonary capillary wedge, heart rate, and arterial pressure (Fig. 1). The stroke index decreased and the systemic vascular resistance increased in four of the five patients in whom they were measured, and remained unchanged in the other patients (Fig. 1). The initial changes in pressures and heart rate, in every instance, were present before the onset of pain for an average period of three minutes (range one to eight minutes) (Fig. 2). The increases in heart rate, pulmonary arterial pressure, and arterial pressure were virtually simultaneous in all patients. In general, there was a further increase in these variables after the onset of pain (Fig. 2). Compared with episodes of resting angina not associated with meals it was noted that changes in pulmonary arterial pressure, stroke index, and arterial pressure were similar to those observed during postprandial angina. The increases in heart rate were, however, more striking during postprandial angina than those in spontaneous angina (Fig. 3).

The electrocardiographic abnormalities indicative of ischaemia, ST depression greater than 1 mm in five patients, and ST elevation greater than 1 mm in another patient, developed at the onset of haemodynamic changes preceding or following them by intervals no longer than 60 seconds.

Except for one patient (case 4), in whom angina was relieved spontaneously (Fig. 3), all patients obtained prompt relief with glyceryl trinitrate administered sublingually. At the point of total pain relief, changes in heart rate, arterial pressure, and pulmonary arterial pressure were reversed. Electrocardiographic abnormalities reverted to those present during the pre-anginal phase.

Discussion

The most prominent haemodynamic changes found in this study in patients with documented coronary artery disease were significant increases in cardiac output and decreases in systemic vascular resistance about 20 minutes after a meal in the absence of pain. There was also a tendency for the arterial blood pressure to decrease and for the heart rate to increase, and though these changes were not statistically significant, they were similar to the postprandial haemodynamic changes previously reported in normal subjects (Jones *et al.*, 1965), non-cardiac patients (Norryd *et al.*, 1975) as well as in patients with coronary artery disease (Wayne and Graybiel, 1933; Klakeg *et al.*, 1955; Goldstein *et al.*, 1971). The moderate albeit inconsistent increases in heart rate and cardiac output may constitute part of an increased sympathomimetic activity associated with the ingestion of food as has been postulated by some investigators who noted the absence of such a

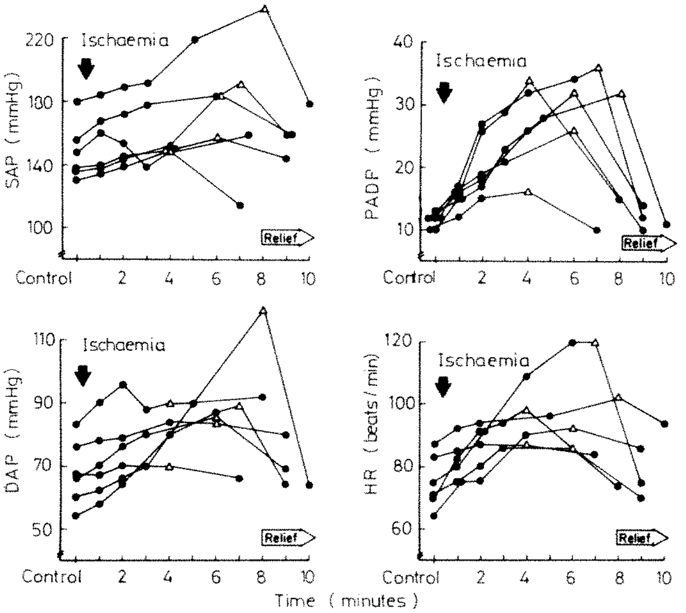

Fig. 2 *The time course of changes in SAP (systemic systolic arterial pressure), DAP (systemic diastolic arterial pressure), PADP (pulmonary artery end-diastolic pressure), and HR (heart rate) in 6 patients during episodes of postprandial angina. Ischaemic changes on the electrocardiogram occurred coincident in time with rises in PADP; changes in other haemodynamic variables supervened somewhat later in relation to the electrocardiographic abnormalities. Though not shown in the figure, the onset of pain invariably* followed *the development of the ischaemic changes.*

response in catecholamine-depleted dogs (Fronek and Stahlgren, 1968). A postprandial increase rather than a decrease or no change in arterial blood pressure has been noted previously in normal subjects (Grollman, 1929; Gladstone, 1935; Dagenais *et al.*, 1966) and in patients with coronary artery disease (Morrison and Swalm, 1940; Berman *et al.*, 1950). It should be emphasised, however, that in these studies measurements were taken at least 45 to 60 rather than 20 minutes after the completion of a meal, which, in addition, had a very much greater caloric content.

The increases in cardiac output found in our patients were associated with a pronounced fall in systemic vascular resistance consistent with peripheral vasodilatation. Such vasodilatation probably involves a number of vascular beds related perhaps to the release of a vasoactive hormone (Norryd *et al.*, 1975); the postprandial increases in flow to different areas such as the liver, kidneys, skin, and especially the splanchnic circulation have, in fact, been documented (Abramson and Fierst, 1941; Brandt *et al.*, 1955; Reininger and Sapirstein, 1957). The increase in cardiac output in our patients was accomplished essentially by an increase in stroke volume which, in the absence of an associated increase in left ventricular filling pressure, is suggestive of an increase in myocardial contractility, though it may simply be the result of a decrease in systemic vascular resistance, the nature of which remains unclear. However, the possibility must also be considered that an augmented venous return may not always be reflected in an increased left ventricular filling pressure if the heart size also increased, a mechanism that could account for the observed changes in cardiac output and stroke. An increase in contractility may also be affected by rises in the levels of serum glucose and fatty acids which, however, were not measured in our study. The relative roles of these various potential mechanisms cannot therefore be evaluated.

In our patients, postprandial angina was associated with haemodynamic changes which differed very much from those occurring in the same patient at the corresponding time after a meal in the absence of angina. During postprandial angina there was an increase in arterial blood pressure, right atrial pressure, and heart rate with striking increases in

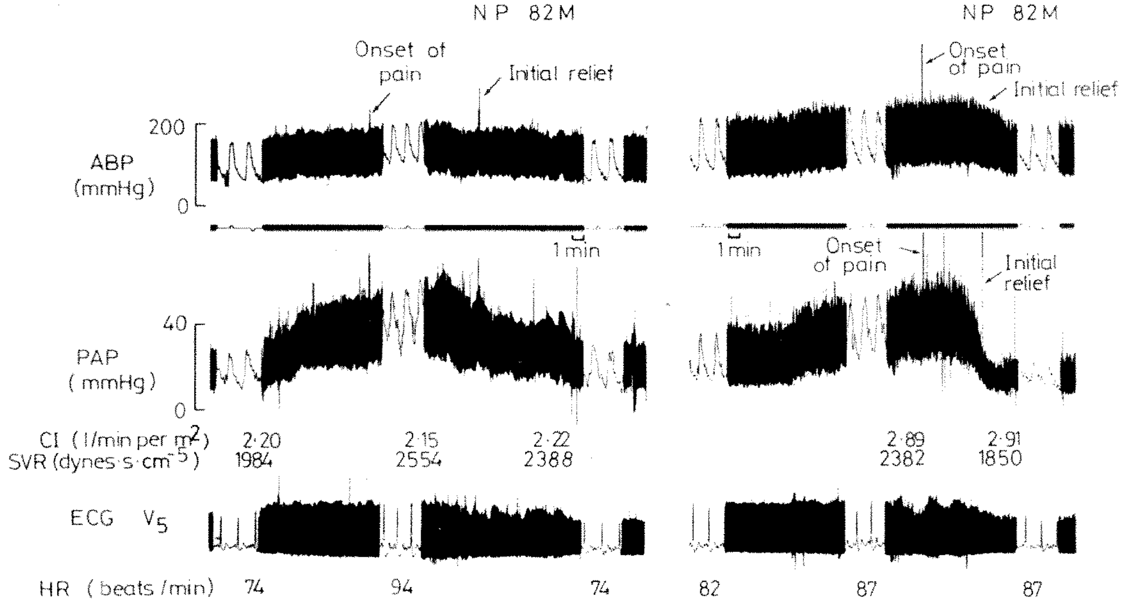

Fig. 3 *Haemodynamic and electrocardiographic recordings during two episodes of postprandial angina in a patient with known ischaemic heart disease. ABP, arterial blood pressure; PAP, pulmonary arterial pressure; CI, cardiac index; SVR, systemic vascular resistance; and HR, heart rate. Note that PAP began to increase before there were changes in HR or ABP and before the onset of pain. Increases in HR, ABP, and SVR occurred with the onset of pain. The panel on the left shows the time course of spontaneous relief of pain; that on the right shows the termination of the episode by glyceryl trinitrate administration.*

pulmonary arterial pressure and pulmonary capillary wedge, and a tendency for the cardiac output to decrease and for the systemic vascular resistance to increase. The concomitant increases in pulmonary capillary wedge pressure and decreases in stroke volume, also encountered in a parallel study in unprovoked or rest angina (Figueras *et al.*, 1978), as well as in exertional angina (Müller and Rørvik, 1958; O'Brien *et al.*, 1969; Lecerof, 1974) are indicative of an acute left ventricular failure. The increases in arterial blood pressure occurred immediately after or at the onset of the ischaemic electrocardiograph abnormalities suggesting that they were more likely to be the result rather than the cause of myocardial ischaemia. In line with this, previous observations in resting angina by us and others (Guazzi *et al.*, 1975; Figueras *et al.*, 1978), as well as in exercise-induced angina (Kattus *et al.*, 1975), have indicated that arterial blood pressure may increase sharply during ischaemia before the onset of pain. Vasopressor reflexes originating from the ischaemic myocardium observed under experimental conditions have been implicated as a possible explanation for these increases in arterial blood pressure (Vatner *et al.*, 1970) but the significance of such reflex activity in man is unclear.

It is of interest that despite the rather low caloric intake and variable composition of the meals, the time of onset of ischaemia in our own studies in man was similar in all the patients studied, as well as in 30 other patients with postprandial angina in whom the study could not be performed. In this respect our findings confirm previous studies that indicated that neither the amount nor the content of the ingested food had significant bearing on the appearance of postprandial angina (Wayne and Graybiel, 1933; Klakeg *et al.*, 1955). Though it has been claimed that, specifically, the ingestion of a large fatty meal is responsible for postprandial angina in some patients, it appears to occur significantly (3–5 hours) later, and it apparently coincides with the peak levels of the plasma triglycerides (Kuo and Joyner, 1955; Friedman *et al.*, 1964). Decreased coronary blood flow by the increased plasma viscosity has been suggested as the mechanism of ischaemia in these cases (Kuo and Joyner, 1955; Regan *et al.*, 1961).

It is now increasingly recognised that many patients with coronary artery disease experience a rest angina unrelated to meals or other precipitating causes; the mechanism here may be related, at least on inferential evidence, to spontaneous decreases in coronary blood flow (Gorlin, 1965; Guazzi *et al.*, 1975; Figueras *et al.*, 1978). The present study suggests that a primary reduction in coronary blood flow may also be responsible for angina that follows meals in patients with coronary artery disease. For example, clear differences were found in the haemodynamic alterations in the postprandial phase in the absence of chest pain and those during postprandial angina in the same patients. Of particular significance was the observation that the double product (SAP × HR) as an index of MVO_2 (Braunwald, 1971), though enhanced after the onset of pain, was altered little or inconsistently *at the onset* of the ischaemic electrocardiographic abnormalities, indicating that an augmentation in the oxygen demand was unlikely to be the primary mechanism of angina in this context. Though our data raise the possibility that postprandial angina may arise on the basis of a primary reduction in coronary blood flow, the nature of such a reduction in myocardial perfusion remains unknown. Coronary vasoconstriction may represent a potential mechanism and it is of interest that gastric distension has been suggested as a possible source of a coronary vasoconstrictor reflex in patients with postprandial angina (Gorlin, 1965). The possibility must also be considered that the development of angina after meals may represent a coincidental occurrence of rest angina, related to intermittent primary alterations in myocardial perfusion in patients with coronary artery disease. Investigations with measurements of myocardial perfusion in patients in whom angina can be produced predictably and repeatedly by a meal are thus likely to provide a more definitive mechanism of postprandial angina.

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Exercise testing in men with significant left main coronary disease[1]

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SUMMARY The exercise tests of 26 male patients with significant left main disease were compared with those of 51 patients with three-vessel disease and 38 patients with two-vessel disease. Exercise-induced ischaemia (chest pain and/or >1 mm ST segment change) occurred in 100 per cent of left main, 69 per cent of three-vessel, and 45 per cent of two-vessel disease patients. Though the mean peak work load was significantly higher in the two-vessel disease group than in those with three-vessel or left main disease, there was a wide overlap between groups. No intergroup differences were found in mean peak heart rates. In patients taking propranolol, no differences in mean peak work loads and heart rates were seen.

The study showed that the absence of an exercise-induced abnormal electrocardiographic response virtually excludes left main disease. As judged by exercise performance, the presence of left main disease did not correlate with the severity of the patient's symptomatology. Propranolol did not influence the frequency of an ischaemic response in patients with left main or three-vessel disease.

Symptomatic patients with significant stenosis of the left main coronary artery are at higher risk of dying than patients without this lesion (Webster *et al.*, 1974; Lim *et al.*, 1975; Conley *et al.*, 1978). It has been clearly established that coronary artery bypass surgery improves survival of these patients (DeMots *et al.*, 1975; Takaro *et al.*, 1976; Campeau *et al.*, 1978). Thus, the identification of the patient with left main coronary stenosis is of paramount importance. Though selective coronary arteriography is the optimal method of determining the presence of this lesion, its expense and potential dangers prevent its routine use for screening the population at risk.

The electrocardiographic response to stress testing has been correlated with the location and severity of coronary disease (Cohn *et al.*, 1972; McHenry *et al.*, 1972; Goldschlager *et al.*, 1976). A very ischaemic electrocardiographic response (>2 mm ST segment depression) has been reported to be a strong indicator of left main disease (Khaja *et al.*, 1974; Cheitlin *et al.*, 1975; Cohen and Gorlin, 1975). However, in many laboratories, including our own, an ST segment change of >1 mm is considered an indication for terminating the exercise test (Blomqvist, 1971). In these laboratories, a change of >2 mm would be rarely seen even when left main disease is present.

Many clinicians have felt that the likelihood of left main disease is correlated with severe symptoms, and the decision whether or not to perform catheterisation, therefore, may be based on the clinical presentation. However, this premise is undocumented. Since the exercise test quantifies the limitations of physical work capacity imposed by typical angina pectoris, a comparison of the exercise test to the presence or absence of left main disease should clarify the supposition that left main disease, symptoms, and limitation to physical activity are correlated.

The purpose of the study was (a) to determine the value of the exercise test in predicting the presence or absence of left main disease, (b) to determine the correlation of the likelihood of left main disease with the severity of symptomatology, and (c) to determine to what extent beta-adrenergic blockade affects the validity of the test.

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Subjects and methods

Between July 1973 and May 1977, 26 male patients with significant left main disease were studied by both cardiac catheterisation and exercise testing in our laboratory. Between July 1976 and May 1977, 51 male patients with significant three-vessel coronary disease and 38 male patients with two-vessel disease were similarly studied by both catheterisation and exercise testing. These patient groups comprised all of the patients studied with a history of chest pain except for patients with electrocardiographic conduction abnormalities or ST segment changes associated with left ventricular hypertrophy. The mean age of the patients in all groups was 51 years.

Long-term oral propranolol was being taken by 7 patients with left main disease, 28 patients with three-vessel disease, and 21 patients with two-vessel disease. No patients were taking other antiarrhythmic treatment or digoxin.

EXERCISE TESTING

Multistage ergometric exercise was performed using a Monark bicycle ergometer (Blomqvist, 1971; Nixon *et al.*, 1978). The test was performed continuously starting at 150 kpm (24·5 watts) with a stepwise load increment increase of 150 kpm (24·5 watts) every 3 minutes. The electrocardiogram was continuously monitored on a Hewlett Packard 1516A tape terminal attached to a Hewlett Packard 1309A oscilloscope, using a modification of Frank's orthogonal lead system (Blomqvist *et al.*, 1965). Permanent recordings at 25 mm/s were made before exercise, during the last 30 seconds of each level of exercise, and during the first 30 seconds of each post-exercise minute of observation for 5 minutes or until the electrocardiogram returned to its pre-exercise configuration. In addition, continuous 5 mm/s recordings were obtained with a Marquette series 330 automatic strip chart recorder as a back-up to the visual monitoring routine. Indirect blood pressure recordings were obtained at 1-minute intervals throughout the study by the Doppler technique, using an Arteriosonde (Roche).

Each exercise test was aimed at 90 per cent of the patient's maximal predicted heart rate. Indications for premature termination of exercise in this laboratory include typical angina pectoris of any severity, electrocardiographic ST segment changes of 1 mm or greater, hypotension during any stage of exercise, ventricular premature beats occurring at a frequency of greater than 3 per minute, or fatigue requiring cessation of exercise (Blomqvist, 1971).

An electrocardiographic ischaemic response was considered positive if the ST segment depression was >1 mm (0·1 mV) below the level of the ST segment at rest and the depression was sustained for 0·08 second after the J point. The exercise tracings were read independently by at least 2 observers without knowledge of the clinical or catheterisation data of the patients. If a single observer considered the electrocardiographic ischaemic response to be questionable, it was deemed to be negative.

CORONARY ARTERIOGRAPHY

All patients underwent cardiac catheterisation within 3 days of their exercise test. Coronary arteriography was performed selectively by hand injection of Renografin 76 by the Judkins technique. Multiple projection coronary cineangiograms of each coronary artery were recorded on 35-mm Eastman Double X negative cine film by a Roentgen V camera at 60 frames per second.

The cinearteriograms were read independently by at least 2 observers without prior knowledge of the clinical or exercise data of the patients. Any single coronary artery was considered significantly stenosed if the luminal narrowing of the artery or one of its branches over 1·5 mm diameter was greater than 50 per cent of the vessel's diameter. When differences in interpretation existed, the arteriogram was evaluated by a third observer, and a consensus of 3 opinions was obtained.

The overall prevalence of left main disease in this laboratory relative to all studied patients with coronary disease is 9 per cent, which is approximately that found in other laboratories.

DEFINITIONS

The definitions of the terms used in this study are as follows. *Prevalence* is the proportion of patients in any study group who have disease. *Sensitivity* is the proportion of patients with disease who have a positive test. *Specificity* is the proportion of patients without disease who have a negative test. The *predictive value of a positive test* is the probability of patients having disease when the test is positive and may be calculated from the mathematical formula:

$$P(D+/T+) = \frac{P(T+/D+)\,P(D+)}{P(T+/D+)P(D+) + \{1-P(T-/D-)\}\{1-P(D+)\}}$$

where $P(D+)$ is the probability of disease (D) before the test (T) is performed (prevalence), $P(T+/D+)$ is the probability of having a positive test when disease is present (sensitivity), and $P(T-/D-)$ is the probability of having a negative test when the disease is absent (McNeil *et al.*, 1975). The *predictive value of a negative test* is the probability of patients not having disease when the test is negative and, using the same symbols, may be calculated from the formula:

$$P(D-/T-) = \frac{P(T-/D-)\ 1-P(D+)}{P(T-/D-)\{1-P(D+)\} + P(D+)\{1-P(T+/D+)\}}$$

STATISTICAL ANALYSIS

Values are expressed as means ± standard errors of the mean (SE). Data were compared by analysis of variance. When significant differences ($P < 0{\cdot}05$) were found, within-group differences were determined by the Student-Newman-Keuls multiple range test (Zar, 1974).

Results

EXERCISE TESTS

The Table summarises the endpoints of the exercise tests in each patient group. All patients with left main disease had either chest pain or electrocardiographic changes, and all but one of these patients (96%) had electrocardiographic changes. This compared with 35 patients (69%) with three-vessel disease and 17 patients (45%) with two-vessel disease who had either chest pain or electrocardiographic changes. In patients taking propranolol, an ischaemic response to exercise occurred in all 7 patients (100%) with left main disease, 21 patients (75%) with three-vessel disease, and 8 patients (38%) with two-vessel disease. In patients not taking propranolol, an exercise-induced ischaemic response occurred in all 19 patients with left main disease, 14 patients (61%) with three-vessel disease, and 9 patients (53%) with two-vessel disease.

Table *Reasons for termination of exercise in each patient group*

	Left main disease (N = 26)		Three-vessel disease (N = 51)		Two-vessel disease (N = 38)	
		(%)		(%)		(%)
Chest pain or electrocardiographic abnormalities or both	26	(100)	35	(69)	17	(45)
Chest pain	18	(69)	26	(51)	9	(24)
Electrocardiographic abnormalities	25	(96)	24	(47)	12	(32)
Chest pain and electrocardiographic abnormalities	17	(65)	17	(33)	4	(11)
Fatigue	0		16	(31)	21	(55)

Peak heart rates during exercise of all patients are shown in Fig. 1. No significant differences were found between mean values for patients with left main disease (118 ± 4 beats/min), three-vessel disease (114 ± 3 beats/min), or two-vessel disease (120 ± 4 beats/min). Similarly, no significant differences were found between the three groups of patients taking propranolol (left main disease, 110 ± 8 beats/min; three-vessel disease, 104 ± 3 beats/min; two-vessel disease, 106 ± 4 beats/min), or not taking propranolol (left main disease, 120 ± 4 beats/min; three-vessel disease, 125 ± 5 beats/min; two-vessel disease, 138 ± 7 beats/min). In all instances, the spread of the individual data showed considerable overlap between the respective groups.

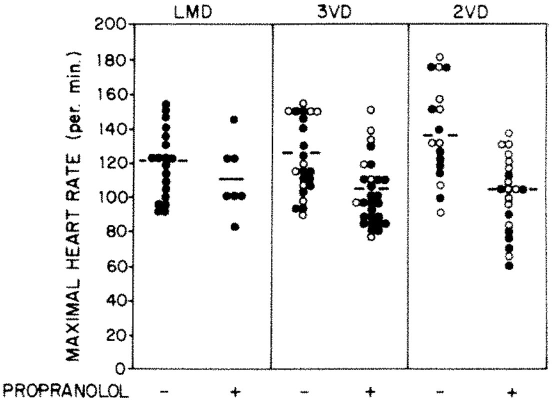

Fig. 1 *Maximal heart rate response (beats per minute) during bicycle exercise in patients with left main disease (LMD), three-vessel disease (3VD), and two-vessel disease (2VD). Patients in each group separated into those taking (+) and not taking (−) propranolol therapy. Closed circles represent patients whose exercise tests were terminated by an ischaemic response (chest pain and/or electrocardiographic abnormalities), and open circles represent those who exercised to fatigue. Solid bars represent mean values.*

The work loads of all patients at the termination of exercise are shown in Fig. 2. Comparison of the mean values of all patients in each group showed significant differences ($P < 0{\cdot}005$). Intergroup analysis determined that while the mean values of patients with left main and three-vessel disease were similar, significant differences were present between values of patients with two-vessel disease (474 ± 27 kpm) and both left main disease (342 ± 29 kpm; $P < 0{\cdot}001$) and three-vessel disease (386 ± 32 kpm; $P < 0{\cdot}01$). Similarly, significant differences were present when the mean peak work loads of patients not taking propranolol were compared ($P < 0{\cdot}005$). Intergroup analysis showed a significant difference between mean values of the left main disease (324 ± 37 kpm) and the two-vessel disease group (504 ± 51 kpm; $P < 0{\cdot}005$). No differences were seen between the left main disease and three-vessel disease (402 ± 22 kpm) or the three-vessel disease

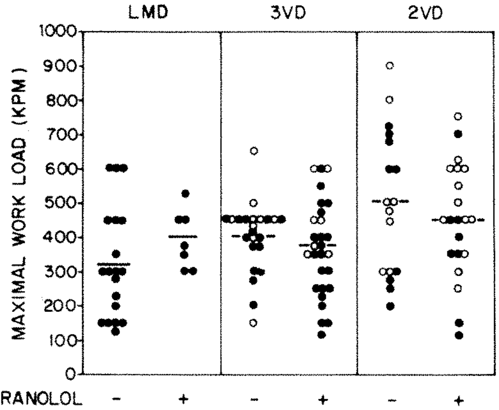

Fig. 2 *Peak work load (kpm) during bicycle exercise in patients with left main disease (LMD), three-vessel disease (3VD), and two-vessel disease (2VD). Patients in each group separated into those taking (+) and not taking (–) propranolol therapy. Closed circles represent patients whose exercise tests were terminated by an ischaemic response (chest pain and/or electrocardiographic abnormalities), and open circles represent those who exercised to fatigue. Solid bars represent mean values (1 kpm = 0·1635 watt).*

and two-vessel disease groups. In patients taking propranolol, no differences were seen in the three groups (left main disease, 393±22 kpm; three-vessel disease, 373±25 kpm; two-vessel disease, 449±37 kpm).

DIAGNOSTIC POWER OF EXERCISE TESTING

When electrocardiographic changes alone were used as the determinant of a postive exercise test, the sensitivity of the test was 96 per cent and the specificity was 60 per cent for patients with left main disease in this group of patients with coronary artery disease. Using this sensitivity and specificity in conjunction with the left main disease prevalence of 9 per cent among all patients with coronary artery disease, the predictive value of a positive exercise test is calculated to be 19 per cent, and the predictive value of a negative test to be 99 per cent. In other words, a patient who has a 9 per cent probability of having left main disease before an exercise test has a 19 per cent probability after a positive test and a 1 per cent probability after a negative test.

When the determinant of a positive exercise test was chest pain and/or electrocardiographic changes at a work load of 300 kpm or less, the sensitivity of the test was reduced to 54 per cent but the specificity increased to 85 per cent. Referring this sensitivity and specificity to the 9 per cent prevalence of left main disease, the predictive value of a positive test was 26 per cent, a small increase over that due to electrocardiographic changes alone. However, the predictive value of a negative test dropped considerably from 99 to 95 per cent.

Discussion

The results of this study confirm that in patients with stable angina pectoris, the exercise test is useful in evaluating the presence or absence of significant left main disease. Conspicuously ichaemic ST segment responses of 2 mm or greater during exercise testing are considered to be very suggestive of left main disease (Khaja *et al.*, 1974; Cheitlin *et al.*, 1975; Cohen and Gorlin, 1975). However, in our laboratory, an ST segment change of 1 mm or greater is taken as evidence of ischaemia and is an indication for termination of exercise (Blomqvist, 1971). Thus, it is pertinent to determine the predictive values of positive and negative tests using this criterion for termination of the test. As one might expect, our study has shown that a positive test will not single out this group of patients. However, the more important question is whether coronary arteriography is necessary purely to determine whether left main disease is present. Our data indicate that the probability of left main disease is only 1 per cent if significant exercise-induced electrocardiographic changes do not occur. Furthermore, not only were all the patients studied male but all had symptoms of chest pain and angiographically documented coronary artery disease. Thus, when referred to the general population, the prevalence of left main disease of 9 per cent used in this study to determine the predictive values of the exercise test is an overestimate and the actual predictive values are even higher.

Several studies have correlated the frequency and magnitude of the electrocardiographic response to exercise with the location and severity of coronary disease (Cohn *et al.*, 1972; McHenry *et al.*, 1972; Goldschlager *et al.*, 1976). Other exercise indices such as threshold heart rates and work loads have been shown to correlate with the extent of coronary disease (Blomqvist *et al.*, 1978; Chaitman *et al.*, 1978; McNeer *et al.*, 1978). Thus, as reported by McNeer and co-workers (1978), patients with left main disease are expected to have more frequent ischaemic responses at lower peak work loads than patients with less extensive disease. In our study, the frequency of an exercise-induced ischaemic response in the respective patient groups concurred with previous findings, being highest in the left main disease group and lowest in the two-vessel disease group. However, peak heart rates and work loads did not correlate as accurately as has been previously reported. When all patients in each group were considered, no significant differences in mean peak heart rates of the three groups were found. Similar statistical analysis of mean peak work loads showed a significant difference only in the two-vessel disease group, with no difference shown between the groups with left main and three-vessel disease. Furthermore, the distribution of threshold work loads of the left main disease patients showed little difference from the patients with three-vessel and two-vessel disease. These latter findings are in line with those of Blomqvist *et al.* (1978), who reported that while group differences existed between left main or three-vessel disease patients when compared with patients with less extensive disease, the wide intra- and intergroup overlap of these exercise measurements precluded a clinical conclusion with respect to any individual patient. In our patients, when 300 kpm was arbitrarily selected as a representative low peak load, the probability of having left main disease after a positive test at this threshold changed a little, whereas the probability of having this lesion after a negative test increased from 1 to 5 per cent. Thus, the presence or absence of an exercise-induced ischaemic response at a lower heart rate or work load failed to distinguish patients with left main disease from those with three-vessel and two-vessel disease.

One possible reason for the differences in our findings compared with other reports may be the inclusion of patients on propranolol therapy. The influence of long-term propranolol treatment on exercise performance and haemodynamics is well known. Though it has a direct depressant action on myocardial contractility, the overall effect of propranolol during exercise is to lower cardiac work by reducing the heart rate and systemic blood pressure response (Wolfson and Gorlin, 1969; Nixon *et al.*, 1978). Furthermore, it has been reported that, in the same patients, angina pectoris was the endpoint of exercise more frequently during the placebo phase than during the therapeutic phase of oral propranolol administration (Alderman *et al.*, 1975). In this latter report, however, the extent of each individual patient's coronary disease was not identified. In other studies correlating the frequency of exercise-induced ST segment changes with the severity of documented coronary artery disease, the effects of propranolol, if any, were either not subject to comment or the patients were excluded from the study (Cohn *et al.*, 1972; Goldschlager *et al.*, 1976; McNeer *et al.*, 1978).

Our data showed that propranolol therapy did not affect the frequency of an ischaemic response in patients with left main disease and three-vessel disease. In patients with three-vessel disease, the frequency was increased in those on propranolol. Conversely, the frequency of an ischaemic response in two-vessel disease patients was less in those on propranolol therapy. However, the significant difference in mean peak work load in patients with two-vessel disease compared with left main and three-vessel disease was abolished by propranolol administration. In addition, there was a wide overlap between each patient group with respect to individual peak work loads and heart rates. Thus, while propranolol did not affect the frequency of an ischaemic response to exercise in patients with more severe and extensive disease, it abolished any differences in other exercise indexes that may be used to distinguish the extent and severity of coronary artery disease.

Many clinicians feel that the incidence of left main disease correlates with the patients' symptomatology. Thus, within the restrictions of the exercise test procedure, an exercise-induced ischaemic response would be expected to occur at a comparatively low work load in these patients (Blomqvist, 1971; McHenry and Fisch, 1977). Our data show that this is not so. There was a wide distribution in individual peak work loads and overlap between each patient group, especially in those patients on propranolol therapy. It seems unlikely that, as judged by exercise performance, the symptoms of an individual patient could be used as an indicator of the presence or absence of left main disease.

This study has shown that, in patients with stable angina pectoris, the exercise test is useful in assessing patients with significant left main disease. The absence of an electrocardiographic response to exercise virtually excludes the possibility of left main disease. Propranolol therapy did not reduce the frequency of an ischaemic response to exercise in patients with left main or three-vessel disease, but abolished any differences in peak work loads that might be useful in distinguishing the extent of a patient's coronary artery disease. The likelihood of the presence of left main disease did not appear to correlate with the severity of the patient's symptomatology as judged by their exercise performance.

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Projection of electrocardiographic signs in praecordial maps after exercise in patients with ischaemic heart disease[1]

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SUMMARY Praecordial surface maps of the electrocardiogram were recorded before and after exercise using 16 electrodes covering the left hemithorax. The ST segment and R and S wave changes were measured in the praecordial maps from 20 individuals with no detectable cardiovascular disease. These showed no significant alteration in ST segments or R/S. In contrast in 40 patients with angiocardiographically proven coronary artery disease it was possible clearly to outline the distribution, severity, and time course of praecordial areas of ST segment depression (36 patients) and ST segment elevation (10 patients). In addition these praecordial areas of ST segment changes were accompanied by a regional and significant fall in the R/S.

The praecordial electrocardiogram with exercise complements the anatomical information obtained from the coronary arteriogram by clearly outlining electrocardiographic projections of regional myocardial ischaemia or cell death.

The exercise electrocardiogram has long been used in the diagnosis and evaluation of patients with coronary artery disease (Bruce and McDonough, 1969; Sheffield and Roitman, 1975; Blackburn, 1977). Interest has centred on ST segment changes on exercise (Roitman *et al.*, 1970; Redwood *et al.*, 1977) though in recent years changes in the QRS vector have been described (Kilpatrick, 1976). Though the praecordial electrocardiogram using 36 to 72 leads is being used to study the natural history of acute myocardial infarction and the effect of interventions (Maroko *et al.*, 1972; Selwyn *et al.*, 1977a; Selwyn and Shillingford, 1977), this technique has not been widely applied to the exercise electrocardiogram. This is the result of difficulties in recording the surface electrocardiogram before transient changes have regressed and in designing an adequate electrode system which is stable during severe exertion. In a recent study, a technique for recording the praecordial electrocardiogram, using conventional equipment available in most hospitals, has been described (Fox *et al.*, 1978). The purpose of the present study is to describe the variety of praecordial electrocardiographic abnormalities that occur on exercise.

Methods

Twenty normal male volunteers (aged 28 to 74, mean 52 years) and 40 consecutive male patients (aged 32 to 72, mean 54 years) with a typical history of angina pectoris, ST segment changes after exercise, and anatomical evidence of coronary artery disease shown by coronary arteriography were studied. Routine 12 lead electrocardiograms were recorded in all patients. All patients were in sinus rhythm at rest. Patients whose electrocardiograms showed abnormalities in the mean frontal axis (that is beyond −30° and +120°) or QRS duration more than 110 ms before exercise were excluded from the study.

Praecordial exercise electrocardiograms were recorded using a direct writing ink jet Mingograf (Elema-Schonander) recording on four channels simultaneously. The gain employed was 10 mm for 1 mV and the paper speed was 25 mm per second. Sixteen points were marked on the chest using an indelible pen, distributed evenly over the left hemithorax as previously described (Fox *et al.*, 1978). Disposable press-stud electrodes were used and secured in position using adhesive tape applied sufficiently tightly to keep the electrodes stable in position but not so as to interfere with respiration. A specially designed switching box (four channels switching four ways) was used in which 16 com-

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mercially available screened electrode cables with press-stud ends were connected to the electrodes. The four unipolar leads of the Mingograf were then plugged into the switching box so that it was possible to record the 16 leads by recording four leads simultaneously and switching through four positions.

Exercise was performed on a bicycle ergometer (Lanooy and Bonjer, 1956). All recordings were made with the patient sitting comfortably, with the arms extended resting on the handlebars. A recording of the 16 leads was made before exercise, immediately after the end of exercise, and then at one minute, three minutes, five minutes, eight minutes, and 10 minutes after exercise. Recordings were then continued at three-minute intervals, as necessary, until the electrocardiogram had returned to normal. While respiratory swing was present in 12 of the 60 patients immediately after exercise, it was possible to overcome this by recording at least three beats during held end-tidal expiration. The electrodes remained in position in spite of maximal exercise. Patients were asked to exercise at a constant rate (50 rpm) and the work load was increased by 25 watts each minute and was continued until the patient was unable to continue because of fatigue, chest pain, or dyspnoea. The presence of multiple ventricular ectopic beats was also an indication to discontinue the test. Exercise was stopped in all the normal controls because of fatigue; the limiting factor in the patients with coronary artery disease was fatigue in six, chest pain in 28, dyspnoea in five, and multiple ventricular ectopic beats in one. The electrocardiogram was monitored throughout the test and resuscitation equipment was available. Connecting up the patient took 10 to 15 minutes and the exercise test and post-exercise recordings 15 to 20 minutes. Each 16-lead praecordial map took about 10 seconds to record.

INTERPRETATION OF RECORDS

The usual criteria for the interpretation of exercise electrocardiograms were applied (Scandinavian Committee on Electrocardiographic Classification 1967). At each of the 16 electrode positions ST segment depression, ST segment elevation, the height of the R wave, and the depth of the S wave were measured in mm. ST segment depression and elevation were measured to the nearest 0·5 mm, using the TP segment as the isoelectric level or the PQ segment when there was no isoelectric TP segment because of tachycardia (Fox *et al.*, 1978). The ST segment was considered to be depressed if there was 1·00 mm or more of shift for at least 0·08 s (Mason and Likar, 1966). ST segment elevation was measured 0·06 s from the end of the QRS complex (Selwyn *et al.*, 1977b), and was ignored if less than 1 mm. None of the patients had ST segments which at rest lay above or below the isoelectric line. The area of ST segment change was defined as the number of praecordial positions that showed ST depression or elevation, and ΣST the sum of the total ST segment depression in

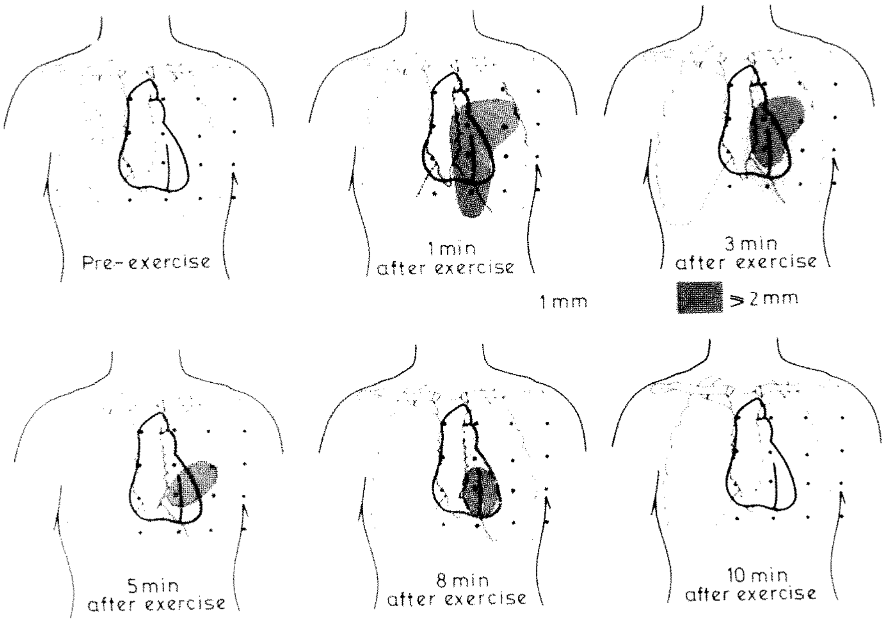

Fig. 1 *A typical example of the sequence of contour maps showing areas of ST segment depression after exercise. A fall in R/S was seen to involve the same areas of the praecordium.*

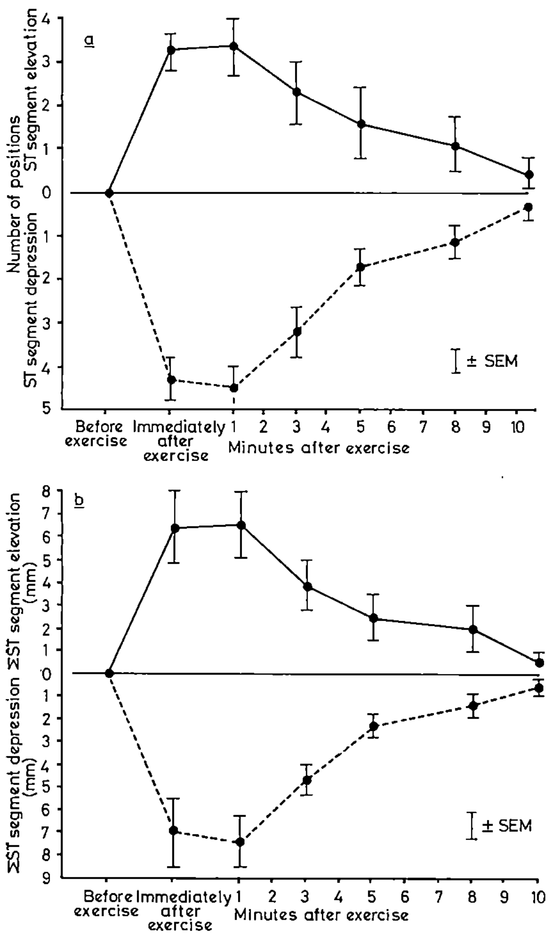

Fig. 2 (a) *The changes seen after exercise in the praecordial area (mean ± standard error mean (SEM)) of ST segment depression (36 patients) and ST segment elevation (10 patients). All patients had angiographically proven coronary artery disease.* (b) *Mean ΣST segment elevation and mean ΣST segment depression in mm ± standard error of mean (SEM) after exercise in the same group of patients.*

mm for all the 16 leads. The arithmetical sum of the height of the R wave and the depth of the S wave (R+S) in mm and the ratio of R to S (R/S) were calculated for each of the 16 positions. The 16 values of R+S and of R/S were added together to produce single values of each variable for each praecordial map ((ΣR+S and ΣR/S). Contour maps of the area of ST segment depression and elevation were drawn for each recording. Q waves were identified using the criteria of the Minnesota Code.

Statistical analysis of the data was performed using Students t test for independent samples.

Results

Of the 40 patients with coronary artery disease, 36 developed ST segment depression alone after exercise. Four patients showed ST segment elevation only, but in six others there was both ST segment depression and ST segment elevation.

Fig. 1 shows the development of praecordial ST segment depression in a patient with critical narrowing of the left anterior descending coronary artery. A fall in ΣR/S occurred immediately after exercise in this patient. The ST segment depression and fall in R/S both involved the same area of the praecordium. Fig. 2a and 2b show the development of praecordial ST segment elevation and ST segment depression that occurred after exercise in the 40 patients with coronary artery disease. These ST segment changes were not seen in the normal controls. Both ST segment elevation and depression followed a similar pattern, being present immediately after exercise and reaching a maximum in terms of both ΣST and area of ST segment change within one minute of the end of exercise. ST segment elevation when present after exercise was found to be confined to the praecordial electrode positions that showed either diminutive R waves ($R/S < 1$) or Q waves.

Fig. 3 shows the R/S ratio changes occurring after exercise in the two groups of patients. A fall in ΣR/S occurred immediately after exercise in the patients with coronary artery disease ($P < 0{\cdot}01$) and

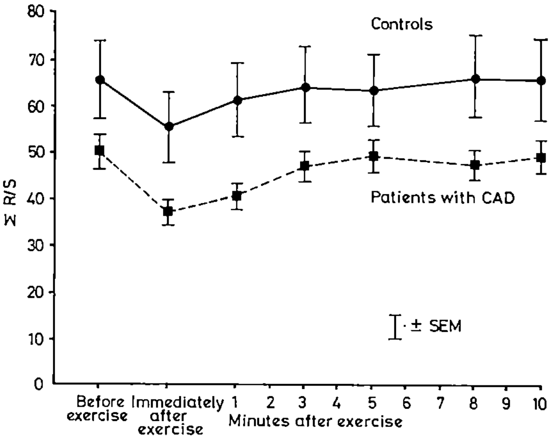

Fig. 3 *The changes seen in the mean ± standard error of mean (SEM) of R/S after exercise in 40 patients with coronary artery disease (CAD) and 20 controls. A significant fall occurred immediately after exercise in the patients with CAD but not the controls.*

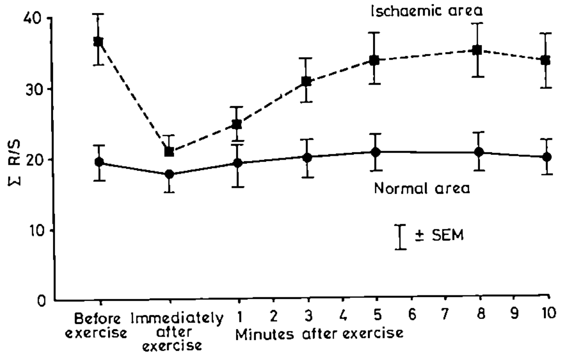

Fig. 4 *Further analysis of the changes in R/S after exercise in 40 patients with coronary artery disease showed that the fall was confined to the praecordial areas that also develop ST segment changes (ischaemic area). A mean R/S ±standard error of mean (SEM) is given for each area.*

in the normal controls, though this fall was statistically significant only in the first group. The mean (±1 standard deviation) ΣR/S for the 20 normal controls was 65·75 ±36·86 before and 55·70 ±34·01 immediately after exercise and for the 40 patients with coronary artery disease was 50·35 ±23·76 before and 37·03 ±16·98 immediately after exercise. Further analysis of the changes in R/S ratio in the patients with coronary artery disease showed that the fall in R/S was greatest in the areas that showed ST segment changes ($P < 0{\cdot}01$) (Fig. 4). The mean (±1 standard deviation) R/S for the areas that showed ST segment change was 36·83 ±22·32 before and 20·86 ±12·62 immediately after exercise and for the remainder of the praecordial map was 19·50 ±15·02 before and 17·78 ±14·90 immediately after exercise. On the other hand there was no significant alteration in either group in the height of the R wave plus the depth of the S wave (ΣR+S) on exercise (Fig. 5). The mean (±1 standard deviation) ΣR+S for the 20 normal controls was 204 ±43·58 mm before and 210 ±38·31 mm immediately after exercise and for the 40 patients with coronary artery disease was 177·2 ±53·20 mm before and 171·9 ±48·76 mm immediately after exercise. One patient with coronary artery disease developed an interventricular conduction defect which was present on all the praecordial leads for one minute after exercise.

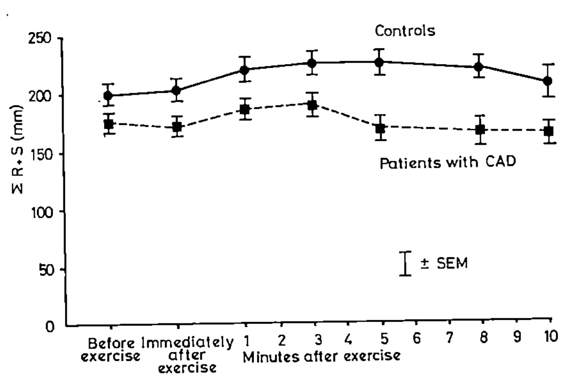

Fig. 5 *The changes seen in the mean ± standard error of mean (SEM) of the praecordial ΣR+S in mm after exercise in 40 patients with coronary artery disease (CAD) and 20 controls. There were no significant alterations in either group.*

Discussion

A non-invasive and physiological means for detecting and assessing myocardial ischaemia may help to rationalise diagnosis and treatment in patients with coronary artery disease. Ideally the investigation should be simple, easily reproducible, and have both a low morbidity and mortality. The exercise electrocardiogram is now an important non-invasive investigation and is used routinely in the diagnosis of chest pain. Initially only single electrocardiographic leads were monitored but in recent years most centres have favoured three leads or even a full 12-lead electrocardiogram (Frank, 1956; Mason *et al.*, 1967).

The praecordial exercise electrocardiogram adds an extra dimension to these tests since it allows a measurement of the area, severity, and time course of electrocardiographic abnormalities that occur after exercise. The semiquantitative assessment which can be made in each patient may help in evaluating medical and surgical treatments. Before praecordial mapping of the exercise electrocardiogram can be used in the diagnosis of chest pain and in the evaluation of medical and surgical treatment, it is necessary to investigate the praecordial electrocardiographic abnormalities that occur in normal subjects and in patients with coronary artery disease. In this study we have investigated the changes that occur on exercise in the ST segment, R/S ratio, and the pattern of the QRS complex (R+S) in the two groups of patients.

Both ST elevation and ST depression occurred after exercise in patients with coronary artery disease. In six patients both were present in the same study. The time course of these electrocardiographic signs after exercise was similar. These changes were not seen in the normal controls.

A small (though not statistically significant) decrease in ΣR/S occurred immediately after exercise in the normal controls. This has been noted previously (Simoons and Hugenholtz, 1975) and, though the cause is not known, it has been suggested that alterations in the haematocrit, changes in the intracardiac blood volume, or temporary increases in the serum potassium level may be responsible. The wide standard deviation found in both groups makes it difficult to apply the information obtained from ΣR/S changes after exercise to individual patients in the diagnosis of coronary artery disease. However, in patients with coronary artery disease a regional decrease in R/S ratio occurred in the areas affected by ST segment change. Since the height of the R wave plus the depth of the S wave did not alter in either group, these alterations in R/S ratio must be the result of a decrease in R wave amplitude plus an equal increase in S wave amplitude rather than a fall in R wave voltage alone. The cause of the regional decrease in R/S ratio is unclear though a localised fall in the isoelectric line, regional dyskinesia, electrolyte or metabolic disturbances may be responsible (Simoons *et al.,* 1977). However, this *regional* alteration in R/S may provide information complementary to that obtained from alterations in the ST segment in identifying patients with coronary artery disease. The ΣR/S at rest was lower in the patients with coronary artery disease than in the normal controls; this is to be expected since eight patients with coronary artery disease had had a previous myocardial infarction.

ST segment elevation was seen after exercise in 25 per cent of the patients with coronary artery disease. This figure is higher than that previously reported using standard exercise tests (Fortuin and Freisinger, 1970), but it is likely that by recording from over the whole of the left hemithorax ST segment elevation on exercise will be seen more often. The underlying pathophysiology responsible for ST segment elevation is unclear. In those patients with both ST segment elevation and depression it is uncertain if these electrocardiographic manifestations are the consequence of reciprocal changes or represent two separate areas of ischaemia (Kleber *et al.,* 1978). Prinzmetal and his colleagues have suggested that ST segment elevation represents localised transmural ischaemia, while ST segment depression occurs as a consequence of patchy ischaemia (Prinzmetal *et al.,* 1961). The conclusions were, however, based on animal experiments and the interpretation of the meaning of these electrocardiographic signs in patients is still controversial.

In conclusion, this study has defined the praecordial changes that occur in the ST segment, and in the R and S waves on exercise. Praecordial surface mapping of the exercise electrocardiogram should, by measuring the changes in the area, time course, and severity of these electrocardiographic signs, help in the diagnosis of chest pain and in the non-invasive assessment of medical and surgical treatment for ischaemic heart disease.

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Vasomotor responses to the Valsalva manoeuvre in normal subjects and in patients with diabetes mellitus

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SUMMARY Cardiovascular responses to the Valsalva manoeuvre were examined in 19 non-diabetic subjects and 32 diabetic patients, some with signs of autonomic dysfunction. All the non-diabetic subjects showed an overshoot in systemic arterial pressure and a bradycardia after the manoeuvre, and in 11 of them only forearm vasoconstriction occurred. However, in eight non-diabetic subjects a forearm vasodilatation was observed at some stage after the Valsalva manoeuvre. Similar patterns of vasomotor responses were seen in some of the diabetic patients. However, those diabetics with postural hypotension showed a systemic arterial hypotension after the Valsalva manoeuvre with no significant change in forearm vascular resistance. Such a response is abnormal but forearm vasodilatation alone may not be.

The Valsalva manoeuvre is routinely used as a means of testing the integrity of cardiovascular reflexes, but the majority of studies have been concerned only with the changes in systemic arterial blood pressure and heart rate evoked by the manoeuvre. Those investigators who have measured forearm blood flow (Sharpey-Schafer, 1953; Roddie *et al.*, 1958; Graf, 1965; Delius *et al.*, 1972) have all reported forearm vasoconstriction after the manoeuvre in normal subjects. The occurrence of a dilatation of the forearm vasculature after the Valsalva manoeuvre has been reported in subjects with autonomic dysfunction (Abboud and Eckstein, 1966; Kontos *et al.*, 1976). In view of the paucity of information about the patterns of vasomotor responses evoked by the Valsalva manoeuvre, we have investigated these in a group of normal subjects, and have compared them with those seen in a group of diabetic subjects, some of whom had evidence of autonomic neuropathy affecting the cardiovascular system.

Subjects and methods

All subjects gave their informed consent to the study which had been approved by the ethical committee. Nineteen normal men aged 18 to 56 years took part in the investigations. They were free of any cardiovascular abnormalities and were not taking any medication. Thirty-two (25 men, 7 women) diabetic patients aged 21 to 64 years were studied. Details of the normal subjects and diabetic patients are given in Table 1, broken down into the groups into which they fell physiologically (see Results).

All studies were carried out between 1400 and 1600 hours in a temperature controlled laboratory set at 22°C. Subjects had only a light snack before attending the laboratory and all insulin-treated patients had had their last injection of insulin at least 6 hours previously. At the time of investigation the diabetes in all patients was well controlled. Before any measurements were made each subject lay quietly on a couch for at least 30 minutes. During this time electrocardiograph electrodes were attached to the chest to provide the input to an instantaneous ratemeter (Devices Ltd.), and a mercury-in-silastic strain gauge was applied to the right forearm to measure blood flow by venous occlusion plethysmography (Greenfield *et al.*, 1963). Arterial blood pressure was measured by auscultation in the left arm. (Systolic and diastolic blood pressures were measured to the nearest 2mmHg. While these measurements were made as precisely as possible, their accuracy depends upon the relation between the true intra-arterial pressures and the pressures measured by auscultation (King, 1967); this relation is not a simple one. King (1967) has reported that indirect measurement of arterial blood pressure, on average, underestimates systolic blood pressure by 4·4 mmHg and overestimates diastolic blood pressure by 12·6 mmHg. However, in our

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experiments the same observer measured the arterial blood pressures in all subjects, thus it is unlikely that random variations in the accuracy of arterial blood pressure measurements could account for systematic differences in calculated forearm vascular resistances.)

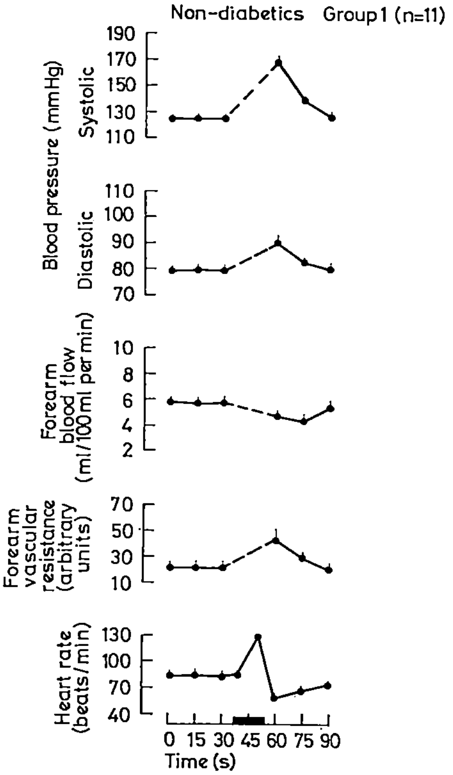

Fig. 1 *Cardiovascular responses to a 15-second Valsalva manoeuvre in 11 non-diabetic subjects (group 1). Forearm vascular resistance was significantly (P < 0·001) raised after the manoeuvre (from 21·3 ± 4·0 units to 42·5 ± 11·0 units) and gradually fell to the control level.*

It was possible to measure heart rate continuously and to obtain simultaneous values of forearm blood flow and brachial arterial blood pressure every 15 seconds. Mean brachial arterial blood pressure ([systolic pressure + 2 (diastolic pressure)]/3) was divided by forearm blood flow to give a measure of forearm vascular resistance. Measurements were made until all variables were steady, and the subject was then asked to perform a Valsalva manoeuvre by blowing a mercury column to a height of 40 mm for 15 seconds. The manometer mouthpiece had a side-arm leak in it to ensure that intrathoracic pressure was persistently raised throughout the manoeuvre. Since meaningful measurements of blood flow could not be made during the manoeuvre, no estimates of forearm vascular resistance could be made during that period. However, measurements of forearm blood flow and systemic arterial blood pressure were made within the 10 second period after the end of the Valsalva manoeuvre, and at 15 second intervals thereafter.

Results were analysed by Student's paired or unpaired t test, as appropriate. Values given in the text are means ± SEM.

Results

Before a full analysis of the results, it was clear that the normal subjects and the diabetic patients fell into three corresponding groups, together with a fourth group of diabetic patients who were obviously different from all others. The results are considered in these physiological groupings.

NON-DIABETIC SUBJECTS

All non-diabetic subjects showed a transient overshoot in systemic arterial pressure and a bradycardia after the Valsalva manoeuvre. However, when patterns of change in forearm vascular resistance were considered, the subjects fell into three groups. Eleven subjects (group 1) had a raised forearm vascular resistance after the manoeuvre and this gradually fell towards baseline levels over the next 30 to 40 seconds (Fig. 1). Four subjects (group 2) initially showed a forearm vasoconstriction which reversed to a forearm vasodilatation, though these changes were not statistically significant (Fig. 2). In the remaining four subjects (group 3) forearm vascular resistance was initially reduced and gradually rose to control levels (Fig. 3).

Because of the small numbers of subjects in groups 2 and 3, possible differences between the control values of the variables measured for the separate groups were not analysed statistically. However, a comparison of those subjects who showed no vasodilatation (group 1) with those who showed a fall in forearm vascular resistance at some stage after the Valsalva manoeuvre (groups 2 and 3) indicated that, though their resting systolic arterial blood pressures were not significantly different (group 1 = 126·5 ± 4·0 mmHg; groups 2 and 3 = 120 ± 3·5 mmHg), they did show a significant (P < 0·01) difference in systolic arterial pressure after the Valsalva manoeuvre (group 1 = 171·7 ± 6·0 mmHg; groups 2 and 3 = 146·9 ± 5·0 mmHg). There was no significant difference between the ages of the subjects in these groups.

DIABETIC SUBJECTS

Not all diabetic subjects showed hypertension and bradycardia after the Valsalva manoeuvre. However, on the basis of changes in systemic arterial pressure and forearm vascular resistance, the diabetics fell into four groups. Thirteen subjects (group 1) showed a post-Valsalva overshoot in arterial pressure and a bradycardia; in this group forearm vascular resistance was initially raised and gradually fell to control levels (Fig. 4). Four subjects (group 2) showed a similar pattern of changes in arterial pressure and heart rate, but in these there was a significant forearm constriction followed by a significant forearm vasodilatation (Fig. 5). In group 3 were 10 subjects who showed a post-manoeuvre overshoot in arterial pressure, but only six of these subjects showed a bradycardia (Fig. 6); however, all subjects in group 3 showed a persistent forearm vasodilatation after the manoeuvre. Five subjects (group 4) showed a significant fall in systolic arterial pressure after the manoeuvre, with no significant change in heart rate or forearm vascular resistance (Fig. 7). These patients were those with postural hypotension (Table 1). Under resting conditions the systolic blood pressure of subjects in group 4 (163·6 ± 15·0 mmHg) was significantly ($P < 0{\cdot}02$) higher than that of the other diabetic subjects (groups 1–3; 131·3 ± 4·3 mmHg) and their forearm vascular resistance was significantly ($P < 0{\cdot}001$) greater (group 4 = 54·4 ± 7·9; groups 1–3 = 29·6 ± 3·4).

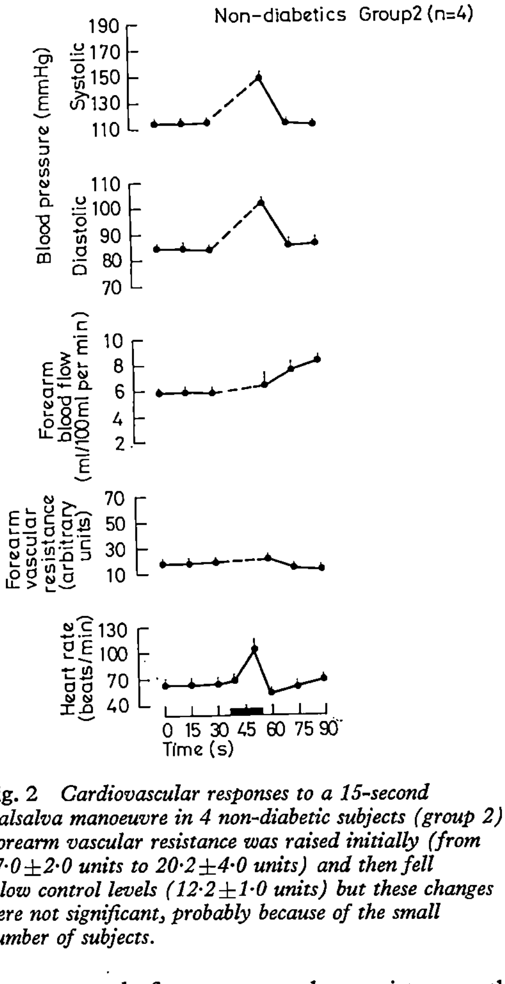

Fig. 2 *Cardiovascular responses to a 15-second Valsalva manoeuvre in 4 non-diabetic subjects (group 2). Forearm vascular resistance was raised initially (from 17·0 ± 2·0 units to 20·2 ± 4·0 units) and then fell below control levels (12·2 ± 1·0 units) but these changes were not significant, probably because of the small number of subjects.*

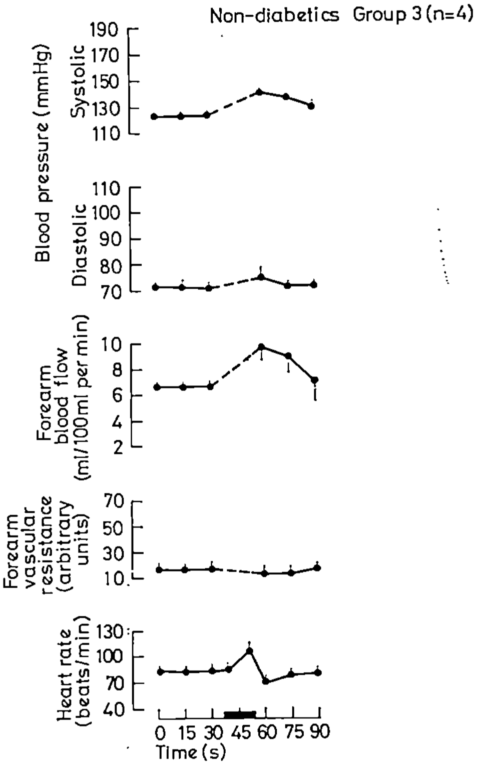

Fig. 3 *Cardiovascular responses to a 15-second Valsalva manoeuvre in 4 non-diabetic subjects (group 3). Forearm vascular resistance was significantly (0·05 > P > 0·02) reduced after the manoeuvre (from 15·7 ± 3·0 units to 11·4 ± 2·0 units) and gradually rose to control levels.*

COMPARISON OF NON-DIABETIC AND DIABETIC SUBJECTS

Excluding diabetics in group 4 who were clearly different from all other groups, there were, none the less, significant differences between the resting levels of systolic arterial pressure, forearm vascular resistance, and heart rate in non-diabetics and diabetics (Table 2). There were no consistent differences between the cardiovascular responses to the Valsalva manoeuvre in the non-diabetics and diabetics in the corresponding groups. In some cases the non-diabetics showed the largest changes (compare Fig. 1 and 4) while in others the diabetics showed the greatest responses (compare the changes in forearm vascular resistance in Fig. 2 and 5).

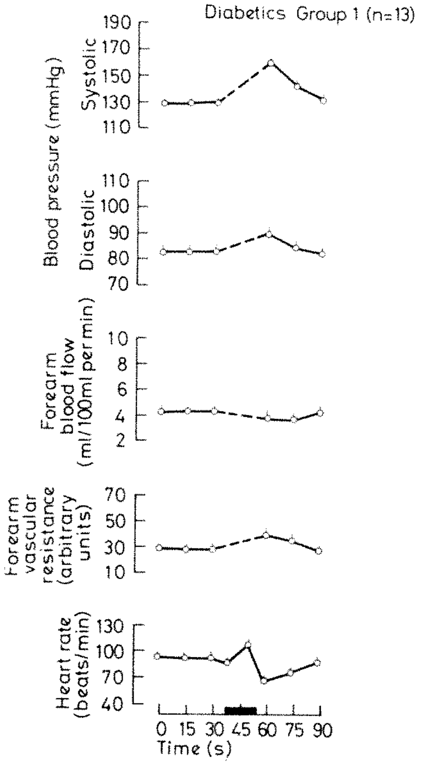

Fig 4 *Cardiovascular responses to a 15-second Valsalva manoeuvre in 13 diabetic subjects (group 1). Forearm vascular resistance was significantly (0·01 > P > 0·001) increased after the manoeuvre (from 27·0 ± 3·0 units to 38·0 ± 4·0 units) and gradually fell towards control levels.*

Discussion

Previous studies on the cardiovascular responses to the Valsalva manoeuvre in diabetes have been confined to a consideration of changes in systemic arterial pressure and/or heart rate (Bennett *et al.*, 1976; Ewing, 1978). The problems associated with quantifying the responses on the basis of heart rate changes alone have been commented upon previously (Bennett *et al.*, 1976, 1978), but generally our findings are consistent with previous reports, where they deal with arterial pressure and heart rate changes.

However, the present observations are new and potentially important because they cause one to question traditional thinking about what constitutes a normal Valsalva response.

As mentioned in the introduction, previous studies on forearm vascular resistance changes in normal subjects in response to the Valsalva manoeuvre have indicated that only a vasoconstriction occurs. However, this classical picture is not readily explained by recourse to the underlying physiology. An increase in central blood volume elicits reflex forearm vasodilatation in man (Roddie *et al.*, 1957;

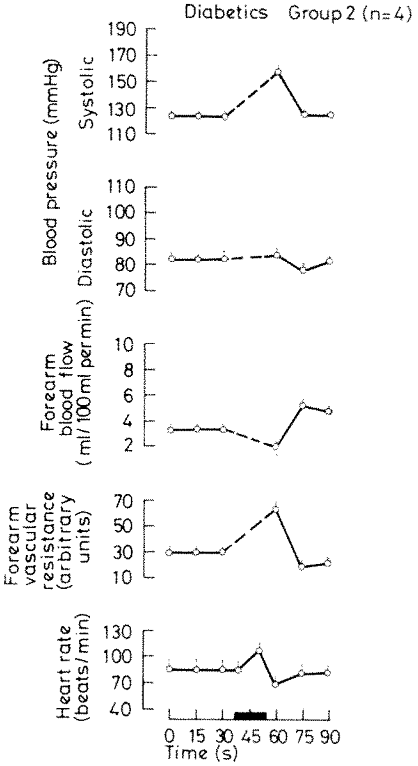

Fig. 5 *Cardiovascular responses to a 15-second Valsalva manoeuvre in 4 diabetic subjects (group 2). Initially, forearm vascular resistance was significantly (P < 0·001) raised after the manoeuvre (from 29·7 ± 2·0 units to 61·0 ± 6·0 units) but then fell below control levels (to 18·6 ± 1·0 units; 0·05 > P > 0·02).*

Brown *et al.*, 1966; Bennett *et al.*, 1979), and after the Valsalva manoeuvre there is an acute increase in central blood volume which would be expected to elicit reflex forearm vasodilatation caused by inhibition of vasoconstrictor tone (Brown *et al.*, 1966).

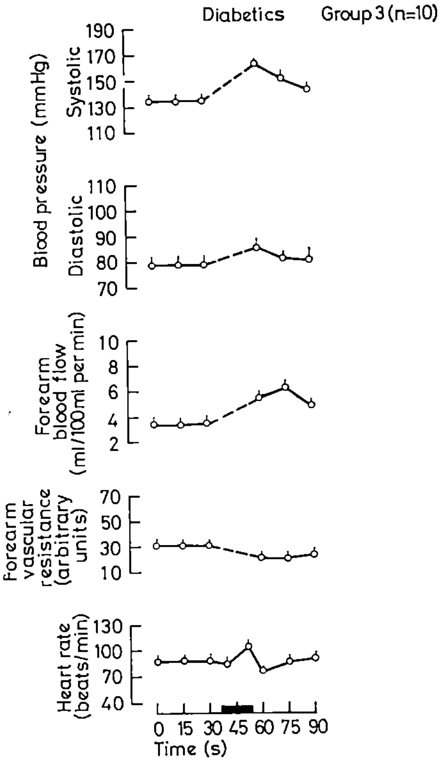

Fig. 6 *Cardiovascular responses to a 15-second Valsalva manoeuvre in 10 diabetic subjects (group 3). Forearm vascular resistance was significantly* ($0{\cdot}05 > P > 0{\cdot}02$) *reduced after the manoeuvre (from 32·2±6·0 units to 22·1±4·0 units) and remained so for some time. In the figure the mean heart rate shown includes those subjects who showed no bradycardia after the manoeuvre; excluding them the post-Valsalva heart rate was 70±4 beats/min.*

Delius *et al.* (1972) estimated forearm vascular resistance and measured action potential discharge in forearm skeletal muscle vasomotor fibres in subjects performing a Valsalva manoeuvre. They found vasomotor nerve fibre discharge was inhibited after the manoeuvre, but vascular resistance remained raised. Delius *et al.* (1972) suggested that the persistence of the forearm vasoconstriction might be the result of 'inertia' in the process of relaxation after intense vasoconstriction, or that it might be the result of a local myogenic response to the raised arterial pressure. However these suggestions are difficult to reconcile with the observation that prolonged periods of forearm vasoconstriction, elicited by reduction in central blood volume, can be followed by distinct reflex forearm vasodilatation (Brown *et al.*, 1966; Bennett *et al.*, 1979). Furthermore, many of the subjects in the present study who showed a forearm vasoconstriction after the Valsalva manoeuvre none the less showed a pronounced forearm vasodilatation after lower body negative pressure (Bennett *et al.*, 1979).

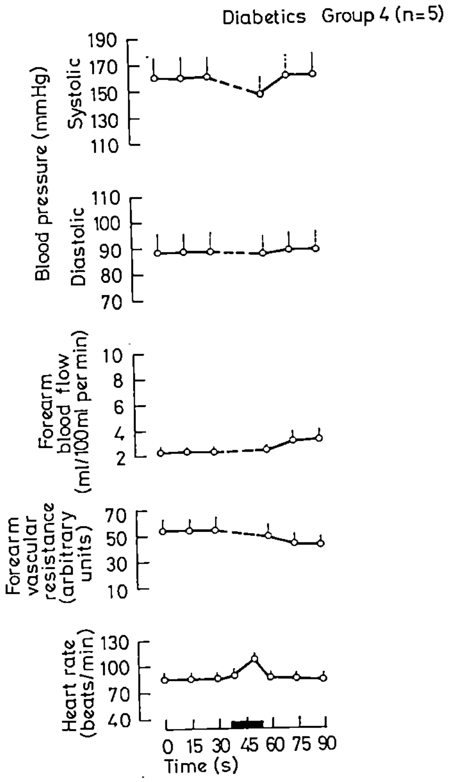

Fig. 7 *Cardiovascular responses to a 15-second Valsalva manoeuvre in 5 diabetic subjects (group 4). After the manoeuvre systolic blood pressure was significantly* ($P < 0{\cdot}05$) *decreased (from 164±15·0 mmHg to 150±13·0 mmHg) and gradually returned to baseline levels. Though the changes in the other measured variables were not significant (probably because of the small size of the group) the pattern of response is clearly different from that of all other groups described.*

Whatever the explanation of the present and previous results, we do not believe that forearm vasodilatation after the Valsalva is of itself an indication of vasomotor abnormality. Such a response was

Table 1 *Details of the normal subjects and diabetic patients studied*

	Group 1 *Normal*	*Diabetic*	*Group 2* *Normal*	*Diabetic*	*Group 3* *Normal*	*Diabetic*	*Group 4* *Diabetic*
Number of subjects	11	13	4	4	4	10	5
Age, mean and range (y)	34 (19–48)	40·0 (30–50)	37 (18–52)	41 (21–56)	48 (31–56)	47 (38–56)	53 (41–64)
Sex	11M	12M, 1F	4M	4M	4M	8M, 2F	1M, 4F
Duration of diabetes, mean and range (y)	—	9 (2–16)	—	10 (0·5–15)	—	12 (6–20)	19 (10–40)
Treatment: Insulin	—	8	—	4	—	7	4
Oral hypoglycaemics	—	5	—	—	—	3	1
Retinopathy: background	—	1	—	—	—	2	1
Haemorrhages and exudates	—	4	—	—	—	1	1
Proliferative	—	—	—	—	—	1	2
Somatic neuropathy	—	3	—	—	—	4	4
Postural hypotension	—	—	—	—	—	—	5
Abnormal (< 5) beat-to-beat variation in heart rate	—	—	—	—	—	4	5

Note that though the corresponding groups of non-diabetic subjects and diabetic patients are fairly well matched for age, the patients in group 4 are, on average, the oldest and have had diabetes longer than the other patients.

seen in 8 out of 19 normal subjects in the present study (considering groups 2 and 3 together). There was no systematic difference between these subjects and those who showed no forearm vasodilatation, except that in the latter the post-Valsalva hypertension was greater and more persistent than in the former, but this would be expected in the absence of reflex skeletal muscle vasodilatation.

The responses of the diabetic subjects in groups 1, 2, and 3 were not consistently different from those of the non-diabetics in the corresponding groups. However, compared with the non-diabetics, a somewhat larger proportion of the diabetics studied showed only forearm vasodilatation after the manoeuvre (31% against 21%), and of these diabetics (group 3) 4 out of 10 showed no bradycardia in response to systemic arterial hypertension. This latter observation is an indication of autonomic neuropathy, perhaps affecting vagal efferent control of the heart (Bennett *et al.,* 1976), and is consistent with the finding that these 4 subjects had abnormally small beat-to-beat variations in heart rate (Bennett *et al.,* 1975, Table 1). Thus, while occurrence of forearm vasodilatation after the Valsalva manoeuvre is not necessarily a sign of abnormality, it does not follow that it indicates normal autonomic nervous function.

Table 2 *Resting cardiovascular variables in non-diabetics (groups 1–3) and diabetics (groups 1–3)*

	Non-diabetics *(n=19)*	*Diabetics* *(n=27)*
Systolic blood pressure (mmHg)	122·3 ±3·6	*131·3 ±4·3
Diastolic blood pressure (mmHg)	78·5 ±3·5	81·7 ±3·8
Forearm blood flow (ml/100 ml per min)	6·1 ±1·1	*3·7±0·3
Forearm vascular resistance (arbitrary units)	18·0 ±3·0	*29·6 ±3·4
Heart rate (beats/min)	75·2 ±5·2	*83·8 ±5·0

*$P < 0·05$.

There were significant differences between the resting levels of cardiovascular variables in the diabetics and non-diabetics in groups 1 to 3 (Table 2). The moderately raised systolic arterial pressure associated with a slight tachycardia and forearm vasoconstriction could have been the result of anxiety in the patients compared with the volunteer subjects. However, it is also possible that such differences were the result of subclinical cardiovascular disease in the patients (Bennett *et al.,* 1979).

The only diabetic subjects whose vasomotor response to the Valsalva manoeuvre was undoubtedly abnormal were those in whom there was a post-manoeuvre hypotension with no significant bradycardia or increase in forearm vascular resistance (though the mean value of the latter was reduced). This pattern of response is similar to that seen in other subjects with signs of autonomic dysfunction (Abboud and Eckstein, 1966; Kontos *et al.,* 1976), and where arterial blood pressure falls but forearm flow increases we agree that the response is abnormal. However, we found that subjects with this pattern of response may none the less show forearm vasoconstriction in response to lower body negative pressure (Bennett *et al.,* 1979) and thus any subject is best investigated using a variety of manoeuvres in order to build up a meaningful profile of the dysfunction.

The resting cardiovascular status of the diabetics in group 4 was very similar to that of patients with borderline hypertension in whom the raised blood pressure appears to be the result of autonomic nervous hyperactivity (Julius and Esler, 1975). However, the response of the diabetics to the Valsalva manoeuvre indicated that autonomic nervous control of the cardiovascular system was impaired. Since the diabetics in this group were those who showed postural hypotension, it is possible that they had increased blood volumes (caused by a renal compensation for the reduction in effective blood volume when upright). A plasma volume expansion could account for the raised systolic blood pressure in the supine position, but it is not clear to what extent this systolic hypertension might have been responsible for the observed abnormalities in cardiovascular control. Eighty per cent of the diabetic patients in group 4 were women, but, on average, they were also older and had had diabetes longer than the patients in the other groups. It is, therefore, impossible from the present results to determine whether or not the abnormalities described are commoner in women.

We are grateful to Professor P. H. Fentem for his constructive criticisms of the manuscript.

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Intracardiac right-to-left shunts demonstrated by two-dimensional echocardiography after peripheral vein injection[1]

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SUMMARY The usefulness of performing real time cross-sectional echo contrast studies, using peripheral venous injections of dextrose 5 per cent in water, for the detection and localisation of atrial and ventricular right-to-left shunts was evaluated in 70 adult patients. Based on their catheterisation data, 20 patients had a shunt at atrial level (group 1) and 14 patients a ventricular septal defect (group 2). Thirty-six patients without a shunt by oximetry served as controls. Echo contrast could not be detected in the left-sided cardiac cavities in any of the control patients.

In 11 of the 15 patients with an uncomplicated atrial septal defect of the secundum type, echo contrast appeared at the left side of the heart and this small right-to-left shunting occurred in systole. Left-sided echo contrast was demonstrated in the 5 patients in whom a bidirectional atrial shunt was found by oximetry.

Of the 14 patients with a ventricular septal defect, 7 had a ratio of right-to-left ventricular pressure exceeding 50 per cent and early diastolic right-to-left shunting of echo contrast was observed in all. This was not seen in any of the patients with an uncomplicated ventricular septal defect.

Diagnostic real time ultrasonic cross-sectional contrast studies can thus be performed in adults using peripheral venous injections of dextrose 5 per cent in water. The presence and timing of intracardiac right-to-left shunts, even when small, are greatly facilitated.

The concept of contrast echocardiography was introduced in the late sixties by Gramiak and his group, primarily to identify intracardiac structures (Gramiak and Shah, 1968; Gramiak *et al.*, 1969; Feigenbaum *et al.*, 1970). Subsequently, intracardiac injections of echo contrast material were found useful in the assessment of congenital heart disease, as a complementary technique to conventional catheterisation methods (Pieroni *et al.*, 1973; Kerber *et al.*, 1974; Seward *et al.*, 1975). Contrast echocardiography found rapid acceptance in the echocardiography laboratory after it was shown by Valdes-Cruz *et al.* (1976) that peripheral vein injection of a Cardiogreen solution produced sufficient ultrasonic contrast to define intracardiac shunts.

The present study was undertaken to evaluate the feasibility and usefulness of performing real time two-dimensional injections of dextrose 5 per cent in water rather than a Cardiogreen solution and to assess its usefulness for the study of intracardiac shunts.

Patients

Real time cross-sectional contrast studies were performed in 70 patients (47 men and 23 women, ages ranging from 17 to 64 years), who were referred to our clinic for cardiac evaluation. All underwent a complete haemodynamic and angiographic study and were divided into 3 main groups.

GROUP 1

This group consisted of 20 patients with an atrial septal defect; in 18 (including 3 patients with Ebstein's anomaly) this was of the secundum type and in 2 of the primum type.

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Table 1 *Data of patients with atrial septal defect*

Case no.	*Age (y), sex, type of ASD*	*Aortic saturation (%)*	*QP/QS*	*RVSP (mmHg)*	*LVSP (mmHg)*	*RVID (mm) M mode*	*Paradoxical septal motion M mode*	*Left-sided echo contrast*
1	19, F, secundum	98	4	47	158	40	Yes	Yes
2	64, F, secundum	90	2·1	112	144	50	No	Yes
3	29, M, primum	89	4	49	165	33	No	Yes
4	24, F, secundum	96	3·8	42	156	30	No	Yes
5	34, F, secundum	95	3·8	42	131	20	No	Yes
6	29, M, secundum	95	3·8	35	124	40	Yes	Yes
7	17, F, primum	97	3·1	32	85	37	No	Yes
8	20, F, secundum	96	2·5	56	136	40	Yes	Yes
9	19, F, secundum	97	4·1	38	144	40	Yes	Yes
10	39, M, secundum	96	2·8	34	143	35	Yes	Yes
11	31, F, Ebstein	91	1·6	22	118	70	Yes	Yes
12	27, M, secundum	95	3·2	88	100	30	Yes	Yes
13	21, M, secundum	97	3·8	34	104	40	Yes	Yes
14	34, F, secundum	96	1·3	22	139	28	No	Yes
15	16, F, Ebstein	92	2·3	34	122	30	No	Yes
16	22, F, Ebstein	84	1·45	18	114	70	Yes	Yes
17	29, M, secundum	95	A+	31	129	40	No	No
18	44, M, secundum	95	3·4	29	171	30	Yes	No
19	21, F, secundum	96	2·4	29	120	36	No	No
20	34, M, secundum	95	4·5	28	128	45	Yes	No

QP/QS, pulmonary-to-systemic flow ratio; RVSP, right ventricular systolic pressure; LVSP, left ventricular systolic pressure; RVID, right ventricular internal diameter; A+, angiographically proven.

GROUP 2

This group consisted of 14 patients with a ventricular septal defect: 7 with an isolated defect (Table 2) and 7 with associated pathology (2 with tetralogy of Fallot, 1 with pulmonary atresia, 1 with truncus arteriosus, 1 with pulmonary hypertension, and 2 with valvar pulmonary stenosis; Table 3). The intracardiac shunt ratios of the patients in both groups were derived from standard formulae (Bing *et al.,* 1947) using values (mean of 3 samples) for systemic and pulmonary arterial and mixed venous oxygen saturations: the latter was calculated from superior and inferior vena cava oxygen contents (Flamm *et al.,* 1969). A summary of these data is presented in Tables 1, 2, and 3.

GROUP 3

This group comprised 36 patients in whom no intracardiac shunt was shown during catheterisation and who served as controls.

Methods

INSTRUMENTATION

Real time cross-sectional ultrasonic studies were performed using a dynamically focused multiscan system (Ligtvoet *et al.,* 1977). The linear array transducer consists of 51 elements of which subarrays of 12 elements are used for both transmission and reception. In transmission, an axicon focus is applied. During reception, 6 zones are sequentially focused and adjusted to the depth from where the echoes originate at that particular moment. The operating frequency is 3·12 MHz. The effective beam width originating from each subarray is 2 mm, yielding a good lateral resolution over the entire

Table 2 *Data of patients with isolated ventricular septal defect*

Case no.	*Age (y), sex*	*Aortic saturation (%)*	*QP/QS*	*RVSP (mmHg)*	*LVSP (mmHg)*	*RVID (mm) M mode*	*Paradoxical septal motion M mode*	*Left-sided echo contrast*
1	24, M	97	1·5	29	125	20	No	No
2	19, M	97	1·5	36	132	15	No	No
3	25, M	97	1·7	29	126	25	No	No
4	19, M	96	1·6	25	140	25	No	No
5	40, F	97	2	34	114	25	No	No
6	30, F	98	1·5	24	140	20	No	No
7	27, F	96	1·2	18	128	20	No	No

QP/QS, pulmonary-to-systemic flow ratio; RVSP, right ventricular systolic pressure; LVSP, left ventricular systolic pressure; RVID, right ventricular septal defect.

Table 3 *Data of patients with ventricular septal defect and associated pathology*

Case no.	*Age (y), sex*	*Associated pathology*	*Aortic saturation (%)*	*PBF / EPBF*	*SBF / EPBF*	*RVSP (mmHg)*	*LVSP (mmHg)*	*RVID (mm) M mode*	*Paradoxical septal motion M mode*	*Left-sided echo contrast*
1	29, F	Pulmonary hypertension	86	1·65	1·57	130	130	—	—	Yes
2	21, F	Operated Fallot with residual shunt	96	3·75	—	51	100	28	No	Yes
3	19, F	Valvar pulmonary stenosis	97	1·5	—	120	124	22	No	Yes
4	51, F	Valvar pulmonary stenosis	90	1·43	1·36	110	124	30	No	Yes
5	22, M	Truncus arteriosus	88	—	—	110	110	37	No	Yes
6	26, F	Pulmonary atresia	78·5	1·5	1·62	145	145	10	No	Yes
7	40, M	Fallot, Potts procedure	90	1·4	1·6	130	140	18	No	Yes

EPBF, effective pulmonary blood flow; PBF, pulmonary blood flow; SBF, systemic blood flow; RVSP, right ventricular systolic pressure; LVSP, left ventricular systolic pressure.

depth of the explored cross-section. Each frame consists of 40 basic lines and the dimensions of the rectangular cross-sectional image are 8 × 16 cm. The system operates at a rate of 50 frames per second. At the bottom of the picture, the electrocardiogram is displayed for timing purposes and its right-hand edge indicates the moment of the stop-frame within the cardiac cycle. Images are recorded on video tape which allows their subsequent analysis in real time, slow motion, or stop-frame. Individual frames can be photographed using instant polaroid photography.

EXAMINATION PROCEDURE

The cross-sectional contrast studies were performed with the patients in the recumbent or slightly left lateral position.

Most attention was given towards visualisation on the left ventricular inflow and outflow portions, since, if any contrast material passed to the left-

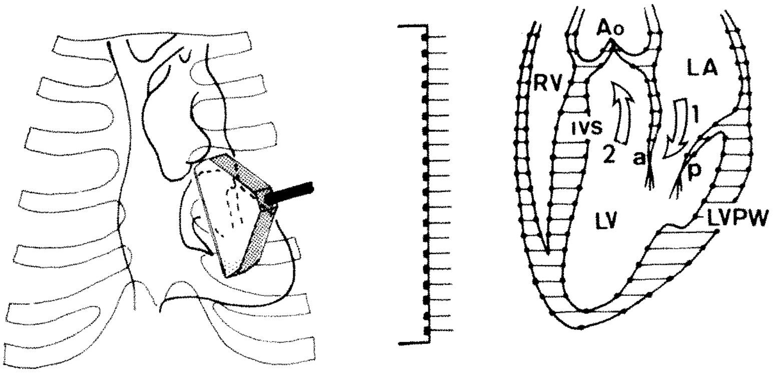

Fig. 1 *The left panel shows the linear array transducer in the position on the chest wall which permits the visualisation of a sagittal cardiac cross-section passing through the long axis of the left ventricle. The right panel is a diagrammatic representation of the left ventricular long axis cross-section. The arrows indicate the left ventricular inflow (1) and outflow tracts (2). Echo contrast is most likely to be detected in these areas when it passes from the right to the left side of the heart.*
Ao, aorta; a and p, anterior and posterior mitral valve leaflets; IVS, interventricular septum; LA, left atrium; LVPW, left ventricular posterior wall; RV, right ventricle.

sided cavities via an atrial septal defect, the chance of identifying it would be greatest in these areas. These structures are best studied in the cross-section following the long axis of the left ventricle which represents the entire M mode echocardiographic view at any given moment within the cardiac cycle (Fig. 1). The interventricular septum is also seen in this cross-section which yields the greatest chance of detecting a right-to-left passage of echo contrast at ventricular level (Roelandt, 1977). A contrast study was considered positive when contrast echoes appeared in the left atrium, left ventricular inflow, and/or outflow tract. To avoid false positive tests as a result of overload effects, great care was taken to use the lowest possible gain settings of the instrument.

ECHO CONTRAST PROCEDURE

After initial standard M mode and cross-sectional analysis, an 18-gauge Teflon venous sheath was inserted into a right antecubital vein. Through this venous route, injections of echo contrast material (5 to 10 ml dextrose 5% in water) were carried out (on average 10 times) while cardiac cross-sections were continuously recorded on video tape. The success rate of obtaining an adequate echo contrast study was 100 per cent.

Results

In the control group of patients with no intracardiac shunt, acoustic opacification remained confined to the right ventricular cavity and outflow tract (Fig. 2). The right-sided contrast effect cleared rapidly, usually after 2 to 5 cardiac cycles, except in patients with tricuspid valve regurgitation, pulmonary regurgitation, or low cardiac output. The findings during ultrasonic contrast studies in the 20 patients with an atrial septal defect (group 1) are given in Table 1. Of these, 15 patients had a classic atrial septal defect of the secundum type and no aortic desaturation was present by oximetry. However, a systolic right-to-left passage of echo contrast material was observed in 11 of these patients at atrial level (Fig. 3).

Five patients of group 1 had in addition to their left-to-right shunt, a right-to-left shunt which was demonstrated by oximetry (aortic oxygen saturation of less than 95%). These 5 patients all showed left-sided appearance of echo contrast (Fig. 4). The

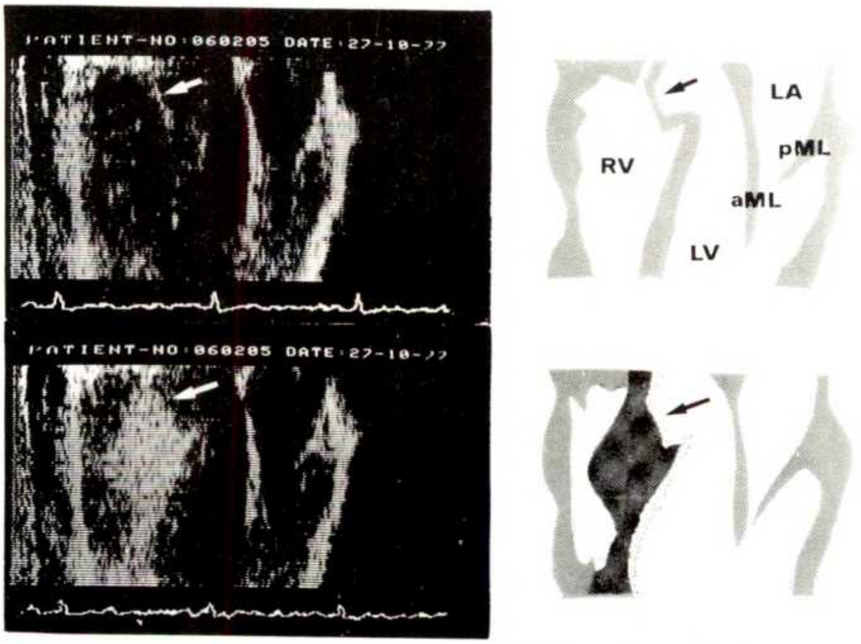
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Fig. 2 *Cross-sectional long axis images of the left ventricle before* (upper frame) *and after peripheral intravenous injection of dextrose 5 per cent in water* (lower frame). *The echo contrast which fills the right ventricular cavity is not detected in the left-sided cavities. The patient had an aneurysm of the membranous interventricular septum* (arrow) *which is delineated by the echo contrast material.*

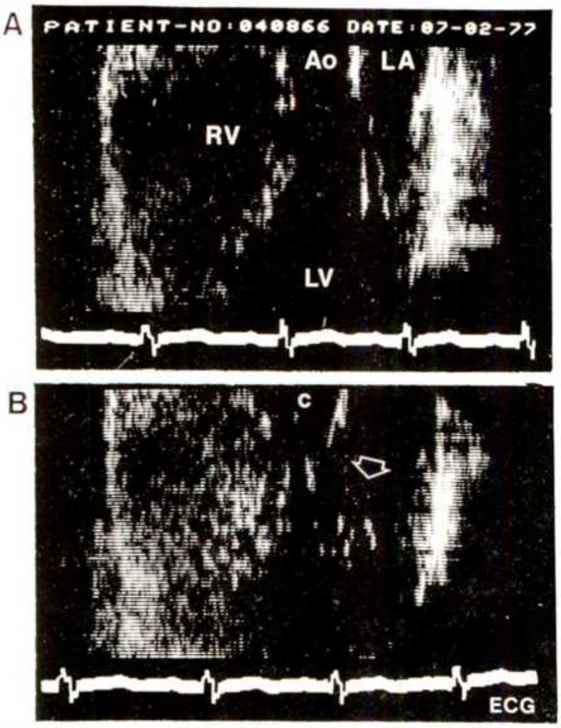

Fig. 3 *Long axis cross-sections of a patient with an atrial septal defect of the secundum type before (frame A) and after peripheral vein injection (frame B). The echo contrast fills the right ventricular cavity (RV) and appears in the left ventricular inflow tract during diastole* (see arrow) *indicating a right-to-left shunt at atrial level. Ao, aorta; LA, left atrium; LV, left ventricle; C, aortic valve cusps*

echo contrast results of group 1 are summarised in Table 4.

In the group of patients with isolated ventricular septal defect and normal right-sided pressures, the echo contrast remained confined to the right ventricular cavity and outflow tract (Table 2).

The 7 patients with ventricular septal defect and associated pathology had in our series a ratio of right-to-left ventricular pressure exceeding 50 per cent. An early diastolic passage of echo contrast from within the right ventricular into the left ventricular outflow tract was demonstrated in all (Fig. 5, 6, and Table 3). In 2 of these patients, the aortic oxygen saturation was greater than 95 per cent.

Table 4 *Left-sided appearance of echo contrast and aortic saturation in 20 patients with atrial septal defect*

Left-sided echo contrast	*Aortic*	*Saturation*
	> 95% *n = 15*	*< 95%* *n = 5*
Present	11	5
Absent	4	0

Discussion

Early studies with ultrasonic contrast were carried out during diagnostic catheterisation, with a catheter tip positioned in a cardiac cavity (Gramiak and Shah, 1968; Gramiak *et al.*, 1969; Feigenbaum *et al.*, 1970; Pieroni *et al.*, 1973; Kerber *et al.*, 1974; Seward *et al.*, 1975). However, this additional information was of relatively low value since traditional techniques, routinely used during catheterisation, already provided the diagnosis.

The advantages of contrast echocardiography became readily accepted as soon as it was shown that the investigation could be performed outside the catheterisation laboratory with a peripheral vein injection (Valdes-Cruz *et al.*, 1976; Seward *et al.*, 1977).

During these studies the ultrasound beam is aimed along one of the standard M mode axes (for example, through the right ventricular outflow tract, aorta, and left atrium) and kept stationary. The appearance of contrast in any of the cavities transected by the sound beam and its timing enables the examiner to study intracardiac blood flow patterns and to deduce the presence and location of a shunt. Using cross-sectional imaging techniques, the entire M mode view rather than the structures along a single sound beam axis is visualised at once. Contrast-filled blood may so be seen to flow through a defect of the atrial or ventricular septum when the appropriate cross-sectional plane is selected for investigation. Direct evidence of the site of the defect may thus be provided. However, the visualisation of the interatrial septum is technically difficult with a linear array transducer of which the versatility in aiming the interrogating cross-section through the cardiac structures from the anterior chest wall is limited. Therefore, we decided to study the inflow and outflow tracts of the left ventricle to show a right-to-left shunt at atrial level. M mode echocardiography was found to be of value for the detection of conditions associated with right-sided volume overload (Popp *et al.*, 1969; Diamond *et al.*, 1971; Kerber *et al.*, 1972; McCann *et al.*, 1972; Tajik *et al.*, 1972a), but its specificity and sensitivity for the diagnosis of an atrial septal defect have been questioned (Tajik *et al.*, 1972b; Hagan *et al.*, 1974; Radtke *et al.*,

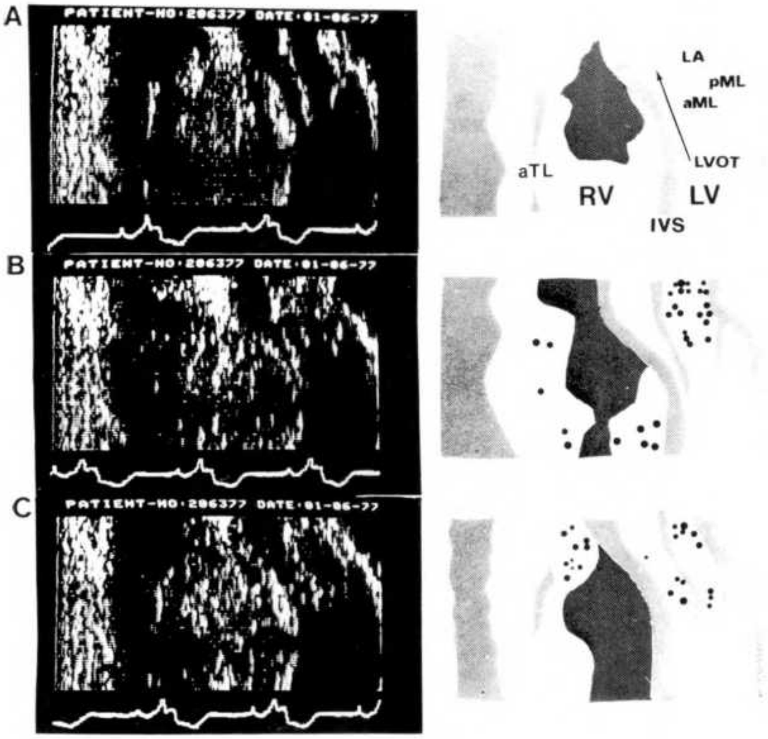
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Fig. 4 *Sagittal long axis cross-section obtained from a patient with Ebstein's anomaly and a right-to-left shunt at atrial level. On frame* A, *one sees ultrasonic contrast filling the dilated right ventricle (RV). On frame* B, *bright specks of echo contrast which accumulated above the mitral valve in early systole pass between the anterior and posterior mitral valve leaflets (aML) and (pML) into the inflow tract of the left ventricle (LV) in early diastole. They are detected in the left ventricular outflow tract (LVOT) at the onset of ventricular contraction (frame* C*).*

1976). Gated B-scan techniques (Matsumoto, 1973; Matsumoto *et al.,* 1975) and real time cross-sectional echocardiography (Dillon *et al.,* 1977; Lieppe *et al.,* 1977) should have several advantages over the M mode method for the direct visualisation of the interatrial septum. However, they may fail to show a localised gap in the mid-portion of the septum in patients with proven atrial septal defect. Furthermore, a false positive diagnosis can be made because 'drop-outs' occur (Roelandt *et al.,* 1976). In other words, structural abnormalities cannot be ascertained unless additional evidence of an abnormal intracardiac flow pattern or the turbulence is obtained. Pulsed Doppler echocardiography (Johnson *et al.,* 1973) and contrast echocardiography offer attractive methods for the demonstration of abnormal intracardiac blood flow patterns (Valdes-Cruz *et al.,* 1976). Some workers have evaluated the diagnostic value of a negative contrast shadow during diastole in the right atrium after peripheral vein injection of Cardiogreen (Dillon *et al.,* 1977). Here, the left-to-right flow of echo-free blood causes a filling defect at the level of the atrial septal defect in the opacified right atrium.

Detailed physiological studies with atrial pressure-flow dynamics, angiography, and dye dilution curves (Swan *et al.,* 1954; Levin *et al.,* 1968; Alexander *et al.,* 1975), have consistently shown minor amounts of right-to-left shunting during early systole in patients with uncomplicated atrial septal defect. The detection of ultrasonic contrast in the left atrium and/or both the left ventricular inflow and outflow chambers can therefore be used as a positive test for the diagnosis of atrial septal defect. In our small group of 20 patients with atrial septal defect, a left-sided appearance of echo contrast could be shown in 16 patients. In the remaining 4, no contrast could be detected, despite repeated studies. Nevertheless, contrast echocardiography appears to be a more sensitive method in demonstrating right-to-left shunting than oximetry since the latter method did not show aortic desaturation in any of these patients. This might be explained by the fact that each microbubble remains a detectable entity wherever it is located in the left atrium, left ventricular inflow, or outflow tracts of which a large volume is explored by cross-sectional echocardiography. On the contrary, detection of oxygen depleted blood is dependent on the volume of right-to-left shunting and also on the position of the catheter tip used for blood

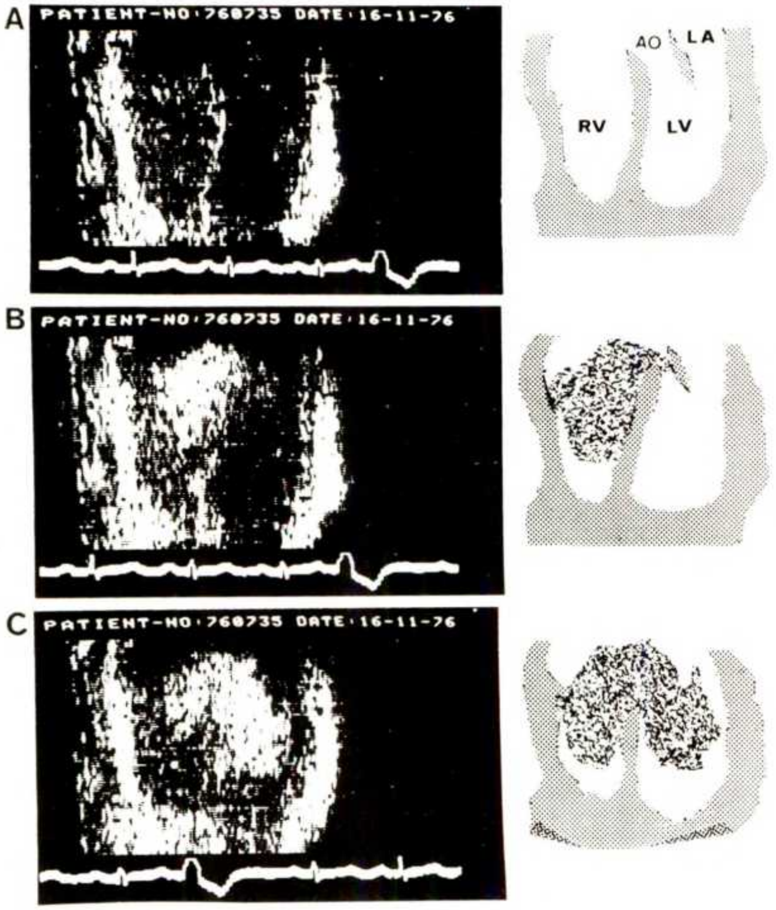
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Fig. 5 *Cross-sections through both the right (RV) and left ventricle (LV) obtained from a patient with ventricular septal defect. Persistent ductus arteriosus and Eisenmenger syndrome before (frame* A*) and after opacification of the right ventricular cavity by echo contrast after peripheral venous injection (frame* B*). The echo contrast passes into the left ventricular outflow tract and left ventricle via the ventricular septal defect in early diastole (frame* C*). Ao, aorta; LA, left atrium.*

sampling. Thus, detection of a few contrast microbubbles by two-dimensional echo is achieved with a higher level of probability.

In patients with a ventricular septal defect, a right-to-left passage of echo contrast occurred in the presence of right ventricular peak systolic pressure above 50 per cent of the left ventricular peak systolic pressure and it appeared in the left ventricular outflow tract early during ventricular diastole (Levin *et al.*, 1967).

Timing analysis disclosed that the shunt flow occurred during the isovolumic relaxation phase, that is after aortic valve closure and before mitral opening (Assad-Morell *et al.*, 1976; Serruys *et al.*, 1977). Two patients failed to demonstrate a detectable oximetric right-to-left shunt, though a few microbubbles in the aorta could be shown. Our study indicates the common occurrence of 'bidirectionality' in uncomplicated atrial septal defect. The demonstration of echo contrast in the left-sided heart chambers can be used as a diagnostic test of an atrial septal defect in patients presenting with non-specific physical examination and M mode findings of right ventricular volume overload. It is helpful to ascertain an atrial septal defect in patients with Ebstein's anomaly. The 'bidirectionality' of the shunt, however, has more serious implications in patients with ventricular septal defects where it indicates a raised right ventricular pressure caused either by pulmonary stenosis or by increased pulmonary vascular resistance.

In conclusion, real time cross-sectional echo contrast studies with peripheral venous injections of 5 per cent dextrose in water have shown that physiological information is obtained together with the actual anatomy of the heart. The demonstration of direction and timing of intracardiac right-to-left shunts, even when small, appears to be greatly

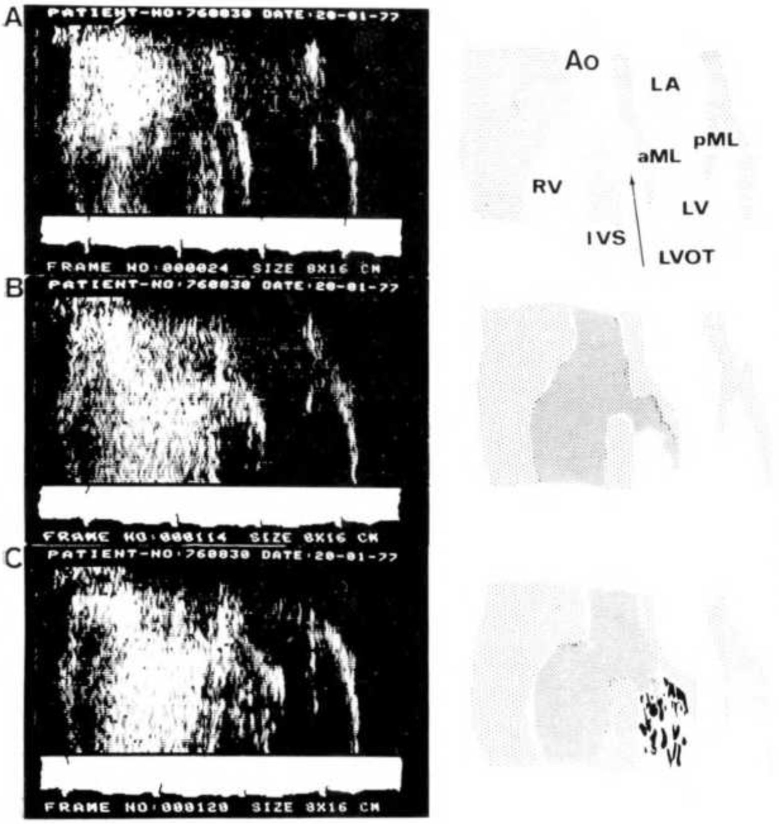
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Fig. 6 *Long axis cross-sections obtained from a patient with truncus arteriosus. The truncus overrides the interventricular septum (IVS) and the left atrium (LA) is dilated (frame* A*). After opacification of the right ventricle (RV), the echo contrast passes into the left ventricular outflow tract (LVOT) in early diastole (frame* B*) where it remains during mid- (frame* C*) and late diastole.*
aML, anterior mitral valve leaflets; pML, posterior mitral valve leaflets.

facilitated. The technique may become the most cost-effective direct method by which to diagnose and localise the site of these intracardiac septal defects non-invasively.

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Effect of ventricular function on left ventricular ejection time in aortic stenosis

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SUMMARY Since recognition of factors which modify the duration of ejection in aortic stenosis is of clinical importance, the relations among rate-corrected left ventricular ejection time, aortic valve area, and determinants of ventricular performance were studied in 54 catheterised patients.

In patients with a normal cardiac index, increasing duration of ejection was linearly related to increasing obstruction. In patients with failing ventricles, on the other hand, the ejection time was less prolonged, and the duration of ejection was unrelated to valve area. At fixed valve area, relation with cardiac output, stroke volume, heart rate, mean aortic valve pressure gradient, mean aortic pressure, and left ventricular end-diastolic pressure could not adequately explain the observed scatter in ejection time. This suggests a multifactorial basis for the wide range of ejection times observed with severe aortic stenosis.

Prolongation of the rate-corrected left ventricular ejection time (LVET) is associated with significant valvular aortic stenosis and is of clinical use in evaluating patients with this disorder (Katz and Feil, 1925; Benchimol *et al.*, 1960; Bonner *et al.*, 1973). Unfortunately, the tendency for the LVET to increase with decreasing aortic valve area is accompanied by a wide scatter of ejection time values, particularly with severe obstruction (Bache *et al.*, 1973; Kligfield *et al.*, 1977). This scatter limits the clinical value of the technique for predicting valve area.

Identification of additional factors which affect the duration of ejection in aortic stenosis is therefore of importance in the evaluation of these patients. For example, it has been shown that though additional aortic regurgitation tends to prolong further the LVET in aortic stenosis, the presence of either coincident significant mitral stenosis or severe mitral regurgitation may normalise the LVET in patients with even severe aortic stenosis (Kligfield *et al.*, 1977).

In heart disorders not affecting left ventricular outflow, LVET shortening is the rule. Though depressed left ventricular function of primarily ischaemic or myopathic aetiology shortens the LVET (Weissler *et al.*, 1961; Heikkilä *et al.*, 1971; McConahay *et al.*, 1972), it has been shown that congestive failure secondary to aortic stenosis is characterised by persistence of LVET prolongation (Bonner and Tavel, 1973). However, despite the expectation that ventricular dysfunction should modify the duration of ejection, the effect of ventricular performance on the LVET in aortic stenosis has yet to be documented and clarified.

Accordingly, we have examined the effect of ventricular function on the prolonged LVET in aortic stenosis with two questions in mind. First, does depressed ventricular performance modify the tendency of LVET to lengthen with increasingly severe obstruction? If so, second, might comparison of LVET at fixed valve area with cardiac output, heart rate, stroke volume, pressure gradient, mean aortic pressure, and left ventricular end-diastolic pressure reveal a determinant of performance that would adequately explain the observed scatter in LVET?

Methods

The records and tracings of 100 catheterised adult patients with valvular aortic stenosis and no additional valve lesions were examined. Of these, 46 were excluded from the study: 27 had technically suboptimal pressure tracings for the purpose of the study, and 19 were excluded because of intraventricular conduction abnormalities (QRS duration

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100 ms) known to affect the time intervals.

The study population thus consisted of 54 adult patients with pure valvular aortic stenosis, no additional valve lesions, normal interventricular conduction, and optimal pressure data. Calculated aortic valve orifice area ranged from 0·2 to 1·4 cm^2.

Left heart catheterisation was performed with Sones catheters via femoral puncture, using a fluid-filled pressure transducer. All pressures used in the calculations were obtained within 10 to 15 beats of left ventricular to aortic root pullback. Right heart catheterisation was performed with Cournand catheters. Cardiac output was calculated from measured, not assumed, oxygen consumption and measured oxygen contents.

LVET was measured in msec from the initial rapid rise to the incisura of the central aortic pressure tracing. The LVET derived from the central pulse has been shown to correlate well with the externally measured carotid ejection time (Weissler *et al.*, 1961; Martin *et al.*, 1971). An average value of four beats was used. Only two patients included in this study were in atrial fibrillation. To minimise the effect of varying cycle length on LVET, only cases in which four cycles of similar length were present, approximating 800 msec, were included, and the average heart rate used for correction. Rate correction was performed according to the standard regression data of Weissler *et al.* (1969): for men, LVET (ms) = measured ejection time (ms) + 1·7 × heart rate.

Valve area was calculated from the standard Gorlin relation, using a constant of 44·5 (Gorlin and Gorlin, 1951).

LVET was compared with calculated aortic valve area for the entire group. To examine the effect of ventricular function on LVET, patients were divided into good ($\geqslant$2·8 l/min per m^2) and poor ($<$2·8 l/min per m^2) function subgroups, where 2·8 l/min per m^2 represents one standard deviation below laboratory mean normal.

To determine whether a single variable of ventricular performance might account for LVET scatter at fixed valve area, the total patient population was divided by valve area: 0·2–0·4 cm^2, 0·5–0·7 cm^2, and 0·8–1·4 cm^2. Within each group, linear regression correlation was sought to relate LVET with either cardiac output, stroke volume, heart rate, mean aortic pressure gradient, mean aortic pressure, or left ventricular end-diastolic pressure.

Results

Rate-corrected ejection times for the total population of 54 patients were plotted against calculated aortic valve areas as shown in Fig. 1. A regression line relating the two variables, LVET = –22AVA + 462, confirms the obvious poor correlation (r = –0·250, P = NS) for the total aortic stenosis population. At any given valve area, a wide range of LVET values exists, suggesting that additional determinants of ejection time are operative. This scatter is most obvious at smaller orifice areas, so that, indeed, no reliable prediction of valve area appears possible for a single LVET determination.

However, when patients were separated by cardiac index into a good function group ($\geqslant$2·8 l/min per m^2) and poor function group ($<$2·8 l/min per m^2), a distinct difference in LVET variation with aortic valve area is seen (Fig. 2). Patients with good ventricular performance tend to have higher values of LVET at smaller valve areas, while patients with poor performance show distinct scatter. As expected, poor ventricular performance was more common at smaller valve area.

In the 20 patients with good ventricular function, LVET lengthened as aortic valve area (AVA) became smaller. The linear regression equation relating the variables, LVET = –49 AVA + 490, reveals significant correlation (r = –0·663, P < 0·01). However, in 34 patients with poor ventricular per-

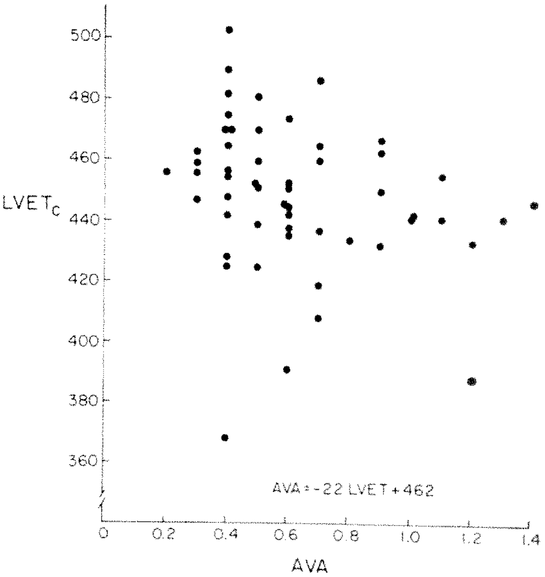

Fig. 1 *Rate-corrected left ventricular ejection time (LVET), in msec, in 54 patients with pure aortic stenosis. Linear correlation with valve area (AVA) is poor for the total group, with wide scatter most apparent at smaller orifice size.*

formance, correlation was poor (r =–0·090, P =NS) for the equation relating LVET with AVA (Fig. 2).

Comparison of the regression lines in Fig. 2 shows that at any given aortic valve area, the ejection time in patients with pure aortic stenosis and good ventricular function tends to be greater than in patients with compromised ventricular performance. In patients with a normal cardiac index, increasing LVET suggests increasing valvular obstruction. For patients with a reduced cardiac index, however, no prediction of valve area is possible from the LVET.

In an attempt to determine which specific determinant of ventricular performance might account for the LVET scatter at fixed valve area, patients were subgrouped by calculated orifice size: 0·2–0·4 cm², 0·5–0·7 cm², and 0·8–1·4 cm². Linear regression equations were calculated for each valve area group and for the total population, relating LVET with cardiac output, stroke volume, heart rate, mean aortic pressure gradient, mean aortic pressure, and left ventricular end-diastolic pressure. The results are shown in the Table. In every case, correlation was poor, with no significant relation found that could explain LVET variance at fixed valve area on the basis of a single measured determinant of ventricular function.

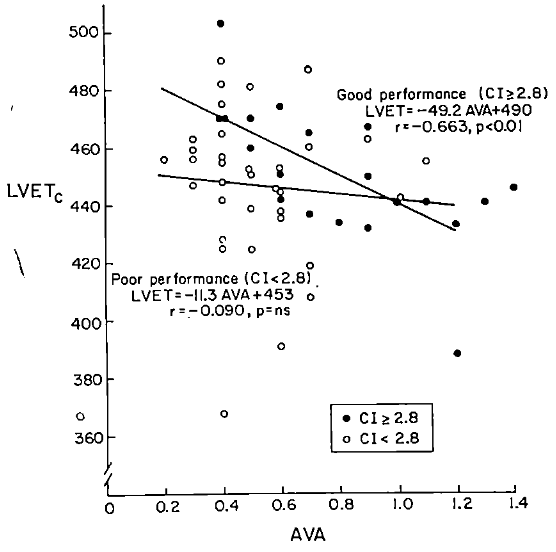

Fig. 2 *Effect of ventricular function. In patients with a cardiac index* $\geq 2{\cdot}8$ *l/min per m² (closed circles), LVET increases as aortic valve area (AVA) decreases, while in patients with poor function (open circles), LVET prolongation is reduced and scatter is obvious. Linear regression relating LVET and AVA demonstrates significant correlation of patients with good function, but no relation in patients with reduced cardiac index.*

Discussion

Since prolonged duration of ejection is a useful sign of valvular aortic stenosis, recognition of factors that modify ejection time in this disorder is of importance. Previous work had documented the significant effect of additional valve lesions on the LVET in aortic stenosis (Kligfield *et al.,* 1977). Though it is generally expected that increasing obstruction be accompanied by increasing LVET, it is well established that ventricular dysfunction of ischaemic or myopathic aetiology shortens the ejection time (Weissler *et al.,* 1968, 1969; Parisi *et al.,* 1971; Bonner *et al.,* 1973). The interaction of these factors requires clarification.

The data in this study demonstrate that at any valve area, the LVET in aortic stenosis tends to be less prolonged in patients with reduced cardiac index. The increasing LVET expected with increasingly severe outflow obstruction is reliably observed only in patients with preserved ventricular performance. In patients with compromised function, no useful prediction of the severity of aortic stenosis is possible based on LVET because of the wide scatter of ejection time in this group.

Variable ventricular performance therefore appears to account for some of the scatter in LVET at fixed valve area seen in this and in previous studies (Bache *et al.,* 1973; Kligfield *et al.,* 1977). This effect of function on the prolonged ejection time in aortic stenosis should be considered in evaluating the LVET in outflow obstruction. Understanding of this LVET effect would be of even greater clinical usefulness in combination with another technique for the estimation of aortic valve area, such as two-dimensional echocardiography, since deviation from expected LVET values might provide quantitative insight into specific aspects of ventricular performance.

Table *Lack of correlation of LVET and individual determinants of LV performance*

	r values (correlation with LVET) Aortic valve area subgroups (cm²)			
	0·2–0·4	*0·5–0·7*	*0·8–1·4*	*Total group*
Cardiac index	0·371	0·372	0·183	0·133
Stroke index	0·182	0·324	–0·178	–0·022
Heart rate	0·194	–0·013	0·265	0·216
LV end-diastolic pressure	0·063	0·072	–0·106	0·099
Mean aortic pressure	0·332	0·069	–0·301	0·022
Mean pressure gradient	0·058	–0·036	–0·044	0·152

It is therefore disappointing that no single index of ventricular function was found to correlate with LVET within narrow valve area groups. Though LVET is significantly dependent on stroke volume, it is also dependent on factors affecting contractility, preload, and afterload (Braunwald *et al.*, 1958; Heikkilä *et al.*, 1971; Martin *et al.*, 1971). For this reason, correlation was sought not only with stroke volume, heart rate, and cardiac output, but with mean aortic pressure gradient, mean aortic pressure, and left ventricular end-diastolic pressure as well. However, no single variable explained the data. Since the range of LVET values found, especially at smaller orifice areas, far exceeds measurement error with this technique, it appears that the effect of function on LVET has a multifactorial basis.

Examination of the Gorlin relation provides an interesting, but speculative, insight into this problem. As is well known, the aortic valve area is calculated from the measured cardiac output, systolic ejection period, and pressure gradient (Gorlin and Gorlin, 1951). Rearrangement of terms and application of the Weissler rate regression data reveals that at a fixed valve area, the rate-corrected

$$\text{LVET} = k' \ \text{SV}/\sqrt{\text{PG}}\ \text{PG} + k'' \ \text{HR}$$

where SV is stroke volume, PG the mean pressure gradient across the aortic valve, HR the heart rate, and k′ and k″ derived constants. From this relation, given the lack of correlation with single variables shown in this study, it appears that the variance of LVET with ventricular function depends on the manner in which heart rate modifies the ratio involving stroke volume and the square root of the pressure gradient. Quantitative investigation of how these relations vary with ventricular performance and valve area should provide further insight into the pathophysiology of aortic stenosis.

Despite the uncertainty about the mechanism, ventricular function is an important modifier of ejection time in aortic stenosis. In patients with a normal cardiac index, increasing duration of ejection is associated with increasing obstruction. In the failing ventricle, on the other hand, ejection time tends to be less prolonged, and the duration of ejection does not reflect the valve area.

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Syndrome of valvular pulmonary stenosis and valvular aortic stenosis with atrial septal defect

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SUMMARY Clinical and morphological findings are described in 2 adults with combined valvular pulmonary and aortic stenosis with atrial septal defect, an extremely rare combination of lesions. The direction of the shunt via the atrial septal defect in this combination appears to be dependent on the relative degree of outflow obstruction on the right side compared with the left side of the heart. In 1 patient the degree of obstruction at the pulmonary valve was nearly three times that at the aortic valve and, therefore, the shunt was right to left and the patient was severely cyanotic. In the other patient, the degree of obstruction at the pulmonary valve was slightly less than that at the aortic valve and, therefore, the shunt was entirely left to right and the patient was acyanotic. Diagnosis of an associated obstructive lesion on the left side of the heart in a patient with an obstructive lesion on the right side of the heart is essential because operative relief of the right-sided obstruction without relief of the left-sided obstruction may lead to rapid, fatal pulmonary congestion.

Isolated pulmonary valve stenosis, with or without patent foramen ovale, is fairly common. Isolated aortic valve stenosis, in contrast, is far more common but associated patency of the foramen ovale is infrequent (Roberts, 1970). Though both as isolated lesions are common, combined pulmonary and aortic valve stenosis in the same patient is extremely rare with or without associated atrial septal defect. This report describes clinical and morphological observations in 2 adults with combined valvular pulmonary and aortic stenosis associated with atrial septal defect, and points out useful findings which should call attention to this unusual combination of lesions.

Case reports

CASE 1

A 33-year-old man was noted to have a praecordial murmur at birth and cyanosis at the age of 6 years. His exercise tolerance was always limited. Examination at the age of 20 disclosed a systolic ejection murmur over the cardiac base and severe clubbing. The haematocrit was 87 per cent. Chest *x*-ray film disclosed the heart and pulmonary vessels to be of normal size, and the electrocardiogram showed right ventricular hypertrophy and a PR interval of 0·28 second. The pressure in the pulmonary artery was 20/10 mmHg; in the right ventricle, 172/18 mmHg; and in the radial artery, 112/86 mmHg. The systemic arterial oxygen saturation was 63 per cent. A left subclavian-to-left pulmonary arterial anastomosis was performed when the patient was 20 years old in 1950.

Thereafter he did well until the age of 28 when exertional dyspnoea returned and it progressively worsened. When admitted to the National Heart Institute in March 1963, severe dyspnoea occurred when walking about 10 paces. A grade 3/6 systolic ejection murmur was audible over the entire praecordium, loudest in the right parasternal second intercostal space. The blood haematocrit was 81 per cent. The electrocardiogram (Fig. 1) showed right axis deviation, bilateral enlargement, right ventricular hypertrophy with strain, and a prolonged (0·28 second) PR interval. At catheterisation, the pulmonary valve could not be traversed by the catheter. The right ventricular pressure was 105/10 mmHg and the right atrial mean pressure was 8, a wave 13, and v wave 9 mmHg. Simultaneous left ventricular and brachial arterial pressures were 142/13 and 85/70 mmHg, respectively. The arterial oxygen saturation was 81 per cent. Cardiogreen dye curves showed a large right-to-left and a smaller left-to-right shunt at the atrial level. Left ventricular angiocardiogram showed a thickened aortic valve with a central jet. The heart

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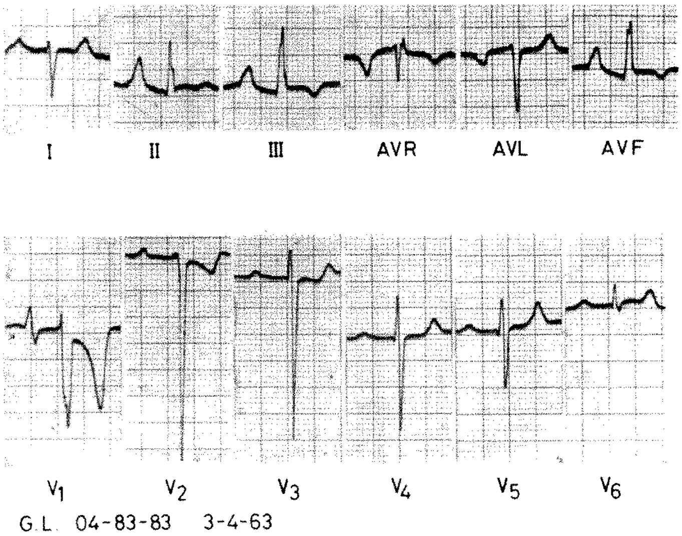

Fig. 1 *Case 1. Electrocardiogram. Note the striking inversion of the T wave in V1, the prominent P waves, prolonged PR interval, evidence of right ventricular hypertrophy, and slight widening of the QRS complexes.*

on chest *x*-ray film was slightly enlarged (Fig. 2), the aorta was elongated and dilated, and the pulmonary vessels were less prominent than normal.

At operation in March 1963, the pericardial space was obliterated by fibrous adhesions and foci of calcific deposits. Numerous collateral vessels were present in the mediastinum and pleura. A thrill was palpated in the ascending aorta. The pulmonary valve was heavily calcified and devoid of an orifice. Portions of the pulmonary valve and of the crista supraventricularis were excised. The large atrial septal defect (Fig. 2) was closed by a Teflon patch containing two perforations 0·6 cm in size. After coming off cardiopulmonary bypass, the pressure in the pulmonary trunk was 15/7 mmHg and in the right ventricle 35/7 mmHg. Simultaneous left ventricular and brachial arterial pressures were 125/15 and 75/40 mmHg, respectively. No procedure was carried out on the stenotic aortic valve. On return to the recovery room, he was hypotensive, despite vasopressors, and died 12 hours later.

At necropsy, 1200 ml blood was present in the pleural spaces. The heart weighed 450 g, the old pulmonary-subclavian arterial shunt was widely patent, the atrial septal patch was intact, and the right ventricular outflow tract and pulmonary valve appeared to be adequately opened (Fig. 2). The aortic valve was three-cuspid, calcified, and stenotic (Fig. 2). The left pulmonary arteries and veins were dilated, whereas those in the right lung had mildly thickened walls.

CASE 2

A 51-year-old white woman had a praecordial murmur at birth. Though always limiting her activities, she was asymptomatic until the age of 50 in 1976 when exertional dyspnoea, easy fatiguability, and pedal oedema were noted. In May 1977, cardiac catheterisation disclosed the following pressures: pulmonary artery, 26/17 mmHg; right ventricle, 128/20 mmHg; simultaneous left ventricle and aorta, 225/26 and 110/70 mmHg, respectively; right atrium, mean 11 with a wave 21 mmHg. A left-to-right shunt of 1·2 to 1 was present at the atrial level.

Examination at the National Heart, Lung, and Blood Institute in November 1977 disclosed fixed splitting of the second heart sound at the cardiac base, a fourth heart sound, and a grade 3/6 holosystolic murmur over the entire praecordium, loudest along the left sternal border. There was mild pedal oedema. The blood haematocrit was 43 per cent. The electrocardiogram (Fig. 3) showed biventricular hypertrophy, atrial abnormality, and indeterminate axis. Chest radiograph (Fig. 3) showed mild enlargement of the cardiac silhouette, dilatation of the ascending aorta, and calcific deposits in the aortic valve. The aortic valve was congenitally bicuspid (Fig. 4) and heavily calcified; it was excised and replaced with a Björk-Shiley prosthesis (size no. 19). The pulmonary valve was dome shaped, had a small central orifice, and was free of gross calcific deposits (Fig. 4). The atrial septal defect consisted of multiple openings in the

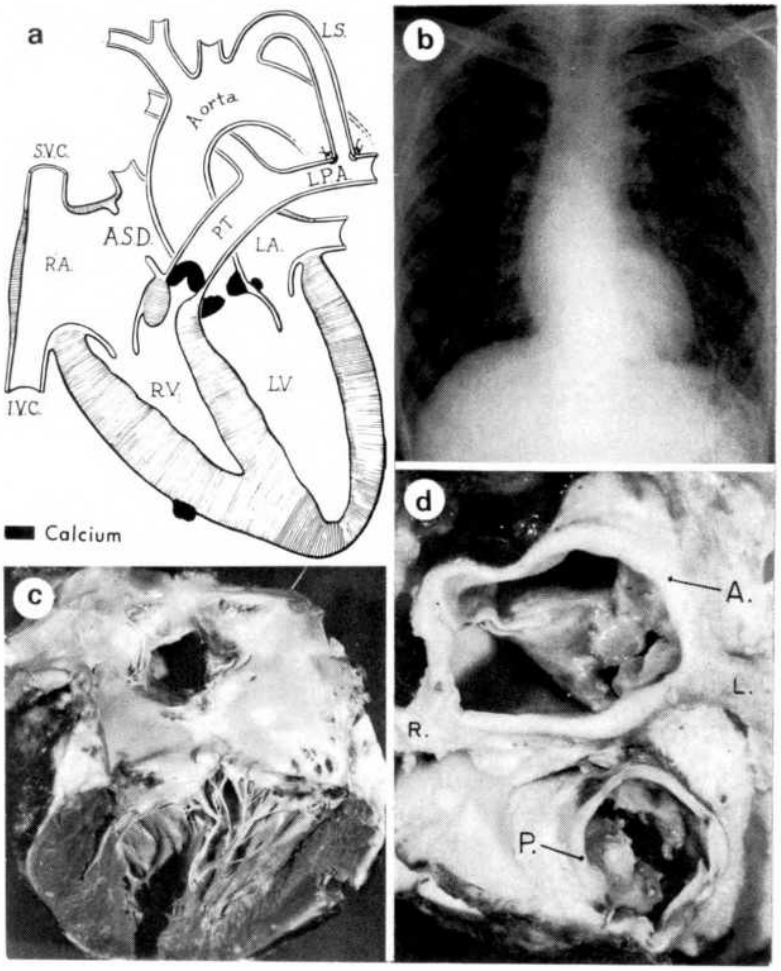

Fig. 2 *Case 1.* (a) *Diagram of heart showing total obstruction of the pulmonary valve and narrowing of the aortic valve. The pulmonary valve had been stenotic but not totally obstructed before the left subclavian (LS) to left pulmonary arterial (LPA) anastomosis 13 years before death. ASD, atrial septal defect; RA, right atrium; RV, right ventricle; PT, pulmonary trunk; IVC, inferior vena cava; SVC, superior vena cava; LA, left atrium and LV, left ventricle.* (b) *Chest* x-*ray film showing elongation of the aorta.* (c) *Opened left side of the heart showing a large secundum type atrial septal defect.* (d) *View of pulmonary (P) and aortic (A) valves from above. The pulmonary one had been opened at operation. R, right and L, left coronary arteries.*

peripheral portions of the fossa ovale membrane and they were closed by multiple sutures. The largest of the openings was 1·0 cm in largest diameter. Measurements of pressures after discontinuation of cardiopulmonary bypass showed a 7 mmHg peak systolic pressure gradient between right ventricular body and pulmonary trunk and no peak systolic pressure gradient between left ventricle and aorta. Her postoperative course was uneventful.

When seen 6 months after operation, she was asymptomatic. Repeat cardiac catheterisation disclosed the following pressures: pulmonary artery wedge mean, 12 mmHg; pulmonary artery, 34/11 mmHg; right ventricle, 38/12 mmHg; right atrial mean, 9 mmHg; and simultaneous left ventricle and aorta 160/20, 152/78 mmHg, respectively. The cardiac index was 2·0 l/min per m^2. No shunt was detected by dye curves.

Comments

The 2 patients described above were adults (33 and 51 years old), both had had praecordial murmurs from birth, both had severe valvular pulmonary stenosis (152 and 102 mmHg gradients), both had considerable valvular aortic stenosis (57 and 115 mmHg gradients), and both had defects in the atrial septum. In case 1, the gradient across the pulmonary valve before operation was nearly 3 times that of the gradient across the aortic valve (152 compared with 57 mmHg) and, consequently, the direction of the shunt across the large atrial septal defect was mainly right to left. In contrast, in case 2, the gradient across the pulmonary valve was slightly less than that across the aortic valve (102 compared to 115 mmHg) and, consequently, the shunt across the atrial septal defect, though small, nevertheless, was entirely left to right.

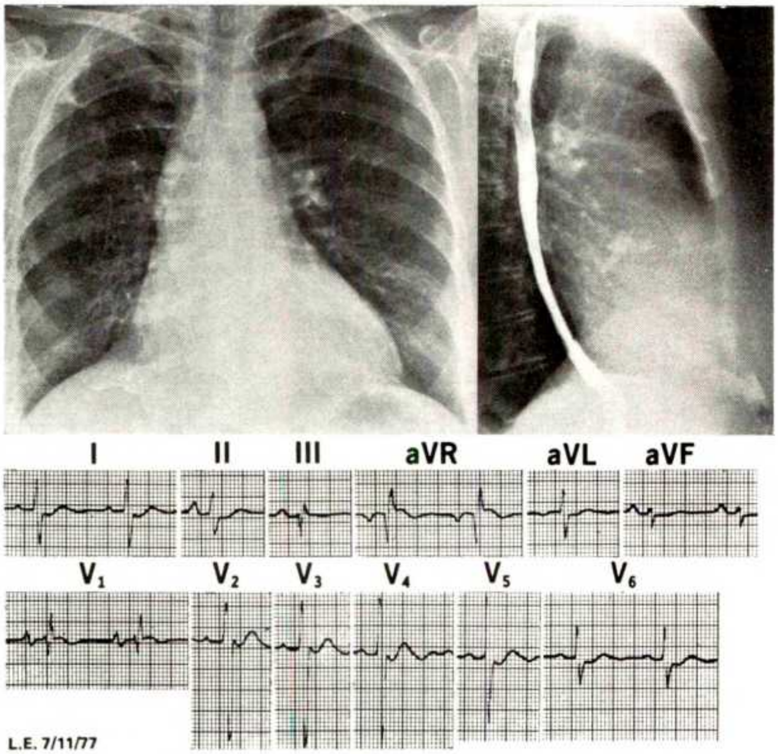

Fig. 3 *Case 2. Chest* x-ray *film* (above) *and electrocardiogram* (below) *each taken a month before cardiac operation. On the lateral view, calcium deposits are discernible in the area of the aortic valve. The electrocardiogram shows biventricular hypertrophy, abnormal P waves, and indeterminate axis.*

When obstructive lesions are present on both sides of the heart, it is essential that both be recognised preoperatively and treated appropriately because relief of the right-sided obstruction without relief of the left-sided obstruction may cause fatal pulmonary congestion (Roberts *et al.*, 1962). In our case 1, the pulmonary valve stenosis was relieved and the atrial septal defect was closed but the aortic stenosis (57 mmHg gradient) was not relieved.

Diagnosis of a left-sided cardiac obstructive lesion in the presence of right-sided obstruction may be difficult. Though present in both patients, dilatation and elongation of the ascending aorta on chest *x*-ray film was the only clinical clue in our case 1 suggesting an obstruction at the aortic valve level. The electrocardiogram in this patient did not show prominence of the left ventricular forces. Diagnosis of the associated aortic stenosis was suspected first at catheterisation after the catheter had crossed the atrial septal defect and entered the left ventricle which had a very high systolic pressure. Diagnosis of an associated left-sided obstructive lesion was more easily recognised in case 2 who had similar degrees of right and left ventricular outflow obstruction, rather than predominant right-sided obstruction as occurred in our case 1. The electrocardiogram in case 2 consequently showed left as well as right ventricular hypertrophy and, in addition, calcific deposits were observed in the aortic valve area by chest *x*-ray film.

Surprisingly, few reports of combined valvular pulmonary and aortic stenosis with or without atrial septal defect have appeared. Horlick and Merriman (1957) described a 4-month-old boy

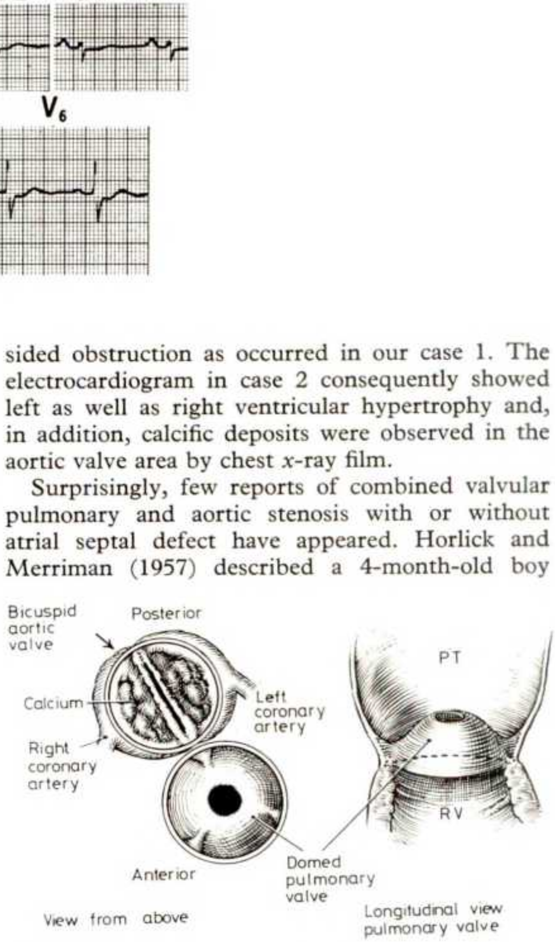

Fig. 4 *Case 2. Diagram showing the stenotic pulmonary and aortic valves from above and the pulmonary valve on longitudinal view.*

with combined valvular pulmonary and aortic stenosis associated with a fossa ovale type atrial septal defect. Thomas (1958) described a 19-year-old man with valvular pulmonary and aortic stenosis associated with a small persistent ductus arteriosus. Sissman *et al.* (1959) described a 5-year-old boy with severe pulmonary stenosis and at operation associated valvular and subvalvular aortic stenosis was recognised. And, finally, Kelly (1965) reported a 28-year-old man with combined valvular pulmonary (60 mmHg gradient) and valvular aortic (110 mmHg gradient) stenosis without an associated shunt.

In contrast to the rarity of combined stenosis at the pulmonary and aortic valve levels, combined *subvalvular* right and left ventricular outflow obstruction and combined pulmonary and aortic *supravalvular* stenosis is not so uncommon. Most of the patients with combined subvalvular obstruction have hypertrophic cardiomyopathy (Neufeld *et al.*, 1960; Maron *et al.*, 1974) and most of the patients with combined supravalvular obstruction have the hypercalcaemic or Williams syndrome (Beuren *et al.*, 1964).

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Evaluation of combined homograft replacement of aortic valve and coronary bypass grafting in patients with aortic stenosis[1]

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SUMMARY Between January 1972 and October 1977, 40 patients with aortic stenosis underwent combined homograft replacement of the aortic valve and coronary artery bypass grafting. There were 29 men and 11 women between the ages of 38 years and 69 years (mean 58 years). Twenty-nine patients (73%) were in class III or IV of the NYHA Classification at the time of operation. Peak systolic aortic valve gradients ranged from 30 to 150 mmHg (mean 77 mmHg). Twelve patients (30%) had triple vessel disease, 13 (33%) had double vessel disease, and 15 (37%) had single vessel disease. Left main stem stenosis was present in four (10%). Altogether 59 grafts were inserted (average 1·5 grafts per patient). There were one early death (2·5%) and two late deaths (5%) during a follow-up between six and 62 months (mean 26 months). Thirty-three patients (89%) moved to class I of the NYHA Classification after operation. Four patients (10%) sustained perioperative infarction without deterioration in clinical status. Nineteen patients were reinvestigated by repeat left ventriculography and by graft and coronary angiography between three and 31 months (mean 12 months) after operation. The overall graft patency rate was 92 per cent. Left ventricular function was assessed by computerised radial analysis of segmental wall motion. Abnormalities of segmental wall motion in 12 patients were improved in eight (75%). All these patients had patent grafts. Deterioration in segmental wall motion occurred in two patients (17%) and was associated with graft occlusion in one and myocardial infarction in the other. In two patients abnormalities of segmental wall motion persisted. Both of these patients had had a myocardial infarction before operation.

Combined homograft replacement of the aortic valve and coronary artery bypass grafting gives good clinical results, with a low early and late mortality. Improvement in left ventricular function occurs in the majority of patients.

Coronary artery disease not uncommonly occurs in patients with aortic stenosis, with a reported incidence varying between 22 and 64 per cent (Basta *et al.*, 1975; Harris *et al.*, 1975; Mandal and Gray, 1976; Moraski *et al.*, 1976; Paquay *et al.*, 1976; Hancock, 1977; Thompson *et al.*, 1979a). Previous studies have shown that isolated valve replacement in such patients may be associated with a high mortality both early and late (Linhart and Wheat, 1967; Linhart *et al.*, 1968). The influence of additional coronary artery bypass grafting on late prognosis and the prevention of myocardial infarction still remains uncertain. The purpose of this paper is to analyse the early and long-term results of this combined procedure in a series of patients with aortic stenosis and to evaluate changes in left ventricular function after operation.

Subjects and methods

Between January 1972 and October 1977, 40 patients with aortic stenosis had operations (by M.Y.) for homograft replacement of the aortic valve and coronary artery bypass grafting at Harefield Hospital or the National Heart Hospital. There were 29 men aged between 38 and 69 years (mean 57 years) and 11 women aged between 38 and 69 years (mean 57 years). All patients were symptomatic and 29 (73%) were in functional class III or IV of the New York Heart Association Classification at the time of

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operation. The duration of symptoms ranged from five to 144 months (mean 40 months). Thirteen patients (33%) presented with angina alone, 25 patients (63%) with angina and dyspnoea, and two patients (4%) with dyspnoea alone. Seven patients (18%) had experienced effort syncope (Table 1).

Table 1 *Presenting symptoms in 40 patients undergoing combined coronary artery bypass grafting and aortic valve replacement*

Symptoms	*No.*	%
Angina alone	13	33
Angina and dyspnoea	25	63
Dyspnoea alone	2	5
Syncope	7	18

The electrocardiogram showed the changes of left ventricular hypertrophy with associated ST-T changes in 29 patients (73%), left ventricular hypertrophy on voltage criteria alone in four patients (10%), and ST-T changes in the absence of left ventricular hypertrophy or digitalis in seven patients (17%). Changes of previous transmural myocardial infarction were present in eight patients (20%) and were anterior in three and inferior in five. Conduction defects were present in seven patients (17%), and included left bundle-branch block in four, right bundle-branch block in two, and bifascicular block in one.

Before operation all patients underwent right and left heart catheterisation after overnight fasting and premedication with atropine 0·01 mg per kg and diazepam 0·15 mg per kg. After measurement of peak systolic aortic valve gradient and left ventricular end-diastolic pressure, cine left ventriculography was performed in the right anterior oblique projection with the injection of approximately 45 ml 70 per cent sodium iothalamate (Conray 420) at 14 ml per second, using a Contrac injector, and filmed at 50 frames per second with an Arriflex camera. Coronary angiography was performed using the methods described by Sones and Judkins. A 70 per cent or greater narrowing of a major coronary artery was taken as evidence of significant coronary artery disease. The haemodynamic findings are summarised in Table 2. Peak systolic aortic gradients varied between 30 and 150 mmHg (mean 77 mmHg). Only four patients had a gradient less than 50 mmHg and all had severe stenosis as judged by a calculated valve area of less than 0·50 cm^2 and low cardiac output (cardiac index less than 2·0 l/min per m^2). No patient had more than mild aortic regurgitation at aortography. Ejection fraction ranged from 0·33 to 0·88 (mean 0·60) and left ventricular end-diastolic pressure from 4 to 30 mmHg (mean 17 mmHg).

Table 2 *Preoperative haemodynamic findings*

Peak systolic aortic valve gradient (mmHg)	30–150 (mean 77)
Aortic valve area (cm^2)	0·30–0·70 (mean 0·52)
Left ventricular end-diastolic pressure (mmHg)	4·0–30·0 (mean 17·0)
Ejection fraction	0·33–0·88 (mean 0·60)
Cardiac index (l/min per m^2)	1·2–4·3 (mean 2·4)

The distribution of coronary artery disease is shown in Table 3. Significant disease was present in the anterior descending artery in 30 patients (75%), in the right coronary artery in 26 patients (65%), and in the circumflex artery in 18 patients (45%). In addition, four patients (10%) had greater than 70 per cent stenosis of the left main coronary artery. Single vessel disease was present in 15 patients (38%), double vessel disease in 13 patients (32%), and triple vessel disease in 12 patients (30%).

Table 3 *Distribution of coronary artery disease*

Coronary artery	*No.*	%
Anterior descending	30	75
Right coronary artery	26	65
Circumflex artery	18	45
Left main stem	4	10

In all patients the aortic valve was replaced by a fresh, unstented, antibiotic sterilised homograft, with continuous coronary perfusion at 30°C (Yacoub *et al.*, 1973). Valve replacement was performed before bypass grafting except in four patients, in whom one of the coronary ostia was too small to permit cannulation. In these patients bypass grafting was performed first and coronary perfusion continued via the bypass graft. Two patients had additional mitral valvotomy and in eight patients a new method of replacing the aortic valve and root was used, with reimplantation of the coronary arteries into the coronary ostia of the homograft valve (Gula *et al.*, 1976). A total of 59 grafts was inserted (average 1·5 grafts per patient) and included 30 to the anterior descending, 20 to the right coronary artery, and nine to the circumflex system. The presence of diffuse peripheral coronary artery disease or failure to opacify the distal coronary vessel at angiography were not regarded as contraindications to bypass grafting. Additional gas endarterectomy was performed in seven patients (18%). The total duration of cardiopulmonary bypass was between 90 and 240 minutes (mean 130 minutes).

Nineteen patients were electively reinvestigated by repeat cardiac catheterisation including coronary and graft angiography, and left ventriculography at times between three and 31 months (mean 12 months) after operation, subject to informed consent. Left ventricular function was analysed before and after operation in these 19 patients by computerised radial analysis of segmental wall motion (Rickards *et al.,* 1977). The cineventriculogram was projected on a Vanguard projector and selected frames digitised with an ultrasonic coordinate convertor (Graf/Pen) on line with an HP 2100A computer. Ejection fraction was determined by the single plane area—length method (Sandler and Dodge, 1968). End-diastolic and end-systolic frames were superimposed using the mid-point of the aortic valve and the geometric centre of gravity of the end-systolic frame as fixed reference points. Radials were automatically plotted from the centre of gravity to the ventricular perimeter at 4° intervals in a clockwise direction starting at the mid-point of the aortic valve. Segmental wall motion was expressed as the percentage shortening along these radials from end-diastole to end-systole, and was plotted against the radial angle (in degrees) around the ventricular perimeter (see Fig. 7). An abnormality was defined as five consecutive radials (20° or 5% of the ventricular perimeter) greater than two standard deviations outside control values obtained from a group of patients with normal ventriculograms. Quantitative changes in segmental wall motion were expressed as changes in the percentage of the ventricular perimeter exhibiting abnormal motion (see Fig. 6). Statistical analysis of data was performed using a one-tailed paired t test. Normalisation of the data by logit transformation before analysis did not influence the result.

Results

There was one early death (2·5%) after operation, and there were two late deaths (5%) during a follow-up period between six and 62 months (mean 26 months). The early death occurred at the time of operation in a patient with poor ventricular function who could not be weaned from cardiopulmonary bypass, despite the use of intra-aortic counterpulsation. This patient had severe left coronary ostial and main stem stenosis with complete occlusion of the right coronary ostium. The two late deaths both occurred at two months after operation, one as a result of Candida endocarditis with subsequent dehiscence of the aortic suture line, and the other as a result of bronchopneumonia. Necropsy in the latter patient showed the graft to be patent and the homograft to be functioning normally. Actuarial analysis of survival in this group is shown in Fig. 1 in comparison to that of 399 patients undergoing isolated, elective homograft replacement of the aortic valve at Harefield Hospital over a similar time period. Neither early nor late mortality at five years were significantly different in the two groups. However, the duration of follow-up in the combined group is shorter and further evaluation is necessary.

All patients were improved after operation and 33 (89%) moved to class I of the New York Heart Association Classification (Fig. 2). Perioperative myocardial infarction, as judged by the appearance of new pathological Q waves or the development of poor R wave progression across the chest leads, occurred in four patients (10%) without mortality or deterioration in clinical status. In three patients the infarct was anterior and in one patient it was both anterior and inferior. The infarct in each case was in the territory of a grafted vessel. Two of these patients were subsequently reinvestigated and in both cases the graft to the infarcted area was found to be patent with good distal run-off; in one there was significant deterioration in left ventricular function. So far no patient has had a late myocardial infarction. Electrocardiographic signs of left ventricular hypertrophy regressed in most patients and the electrocardiogram has returned to normal in 32 patients (86%) (Fig. 3).

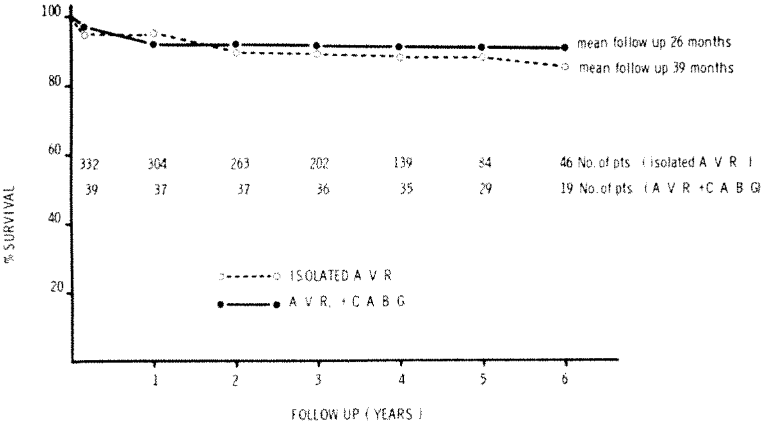

Fig. 1 *Actuarial analysis of survival after combined aortic valve replacement and coronary artery bypass grafting compared with that of 339 patients undergoing isolated, elective aortic valve replacement at Harefield Hospital.*

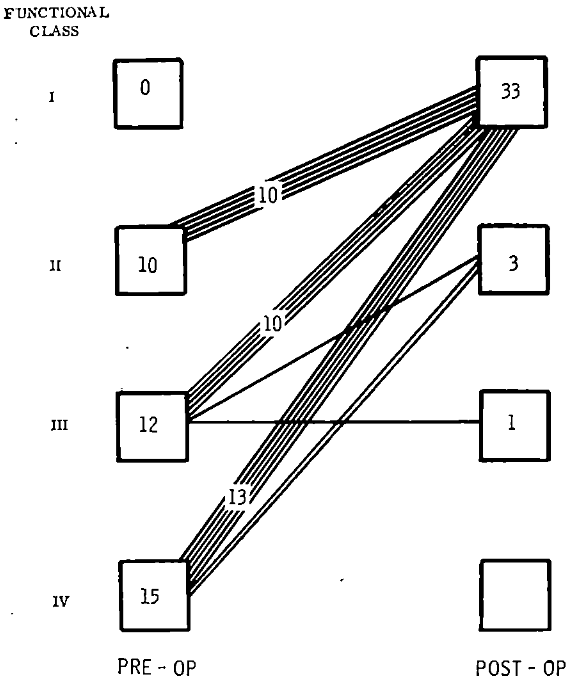

Fig. 2 *Regression of symptoms after combined aortic valve replacement and coronary artery bypass grafting.*

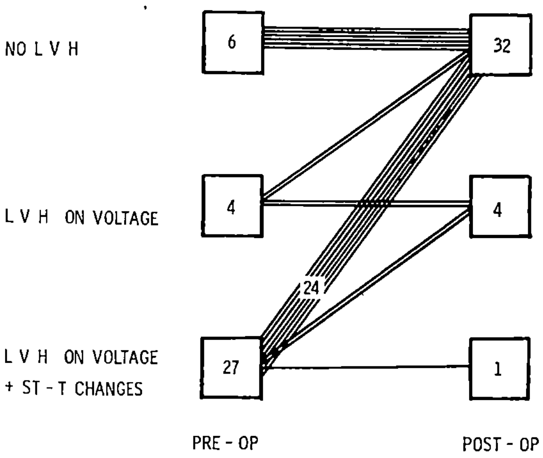

Fig. 3 *Regression of electrocardiographic signs of left ventricular hypertrophy after operation.*

Nineteen patients were reinvestigated at times between three and 31 months (mean 12 months) after operation. Altogether 26 grafts were inserted in this group. At reinvestigation all grafts were entered and 24 (92%) were found to be patent. Graft patency did not appear to be influenced by the particular artery grafted (Fig. 4).

Analysis of the group as a whole showed a significant increase in ejection fraction after operation from a mean of 0·63 to 0·72 ($t=2{\cdot}28$, $P<0{\cdot}025$) (Fig. 5). If this group is divided into patients with a normal preoperative ejection fraction (greater than 0·70) and those with a reduced ejection fraction, there was no significant change in ejection fraction after operation in the former group ($t=0{\cdot}71$, $P>0{\cdot}5$). There was, however, a significant increase in ejection fraction in patients with a preoperative ejection fraction less than 0·70 ($t=3{\cdot}26$, $P<0{\cdot}005$).

In the group as a whole there was also a signi-

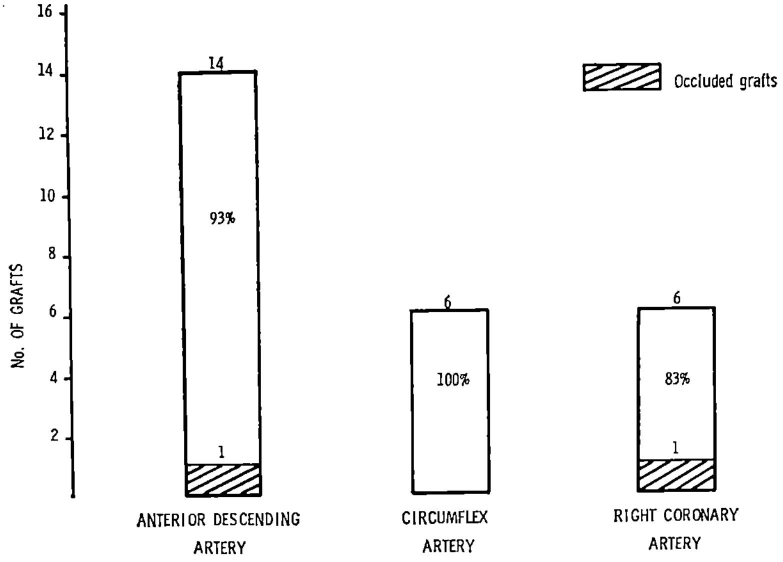

Fig. 4 *Graft patency in relation to the particular artery grafted.*

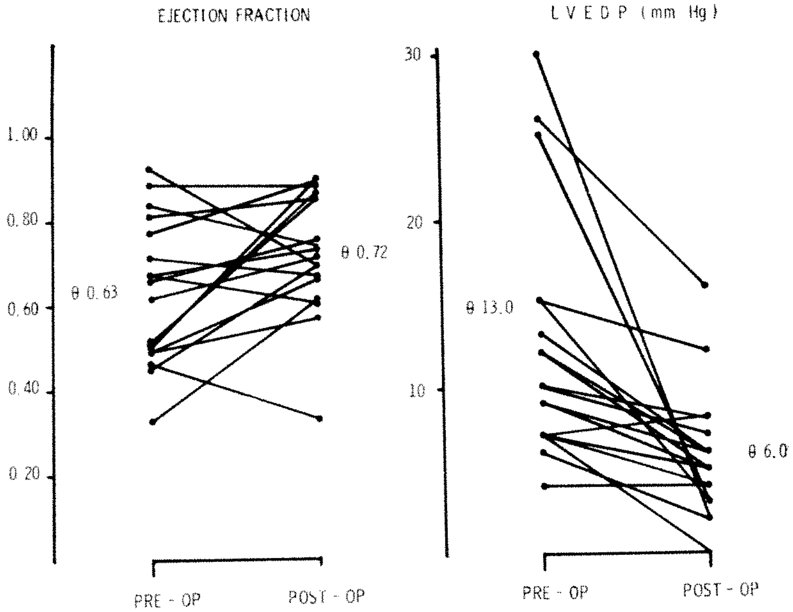

Fig. 5 *Changes in ejection fraction and left ventricular end-diastolic pressure after operation.*

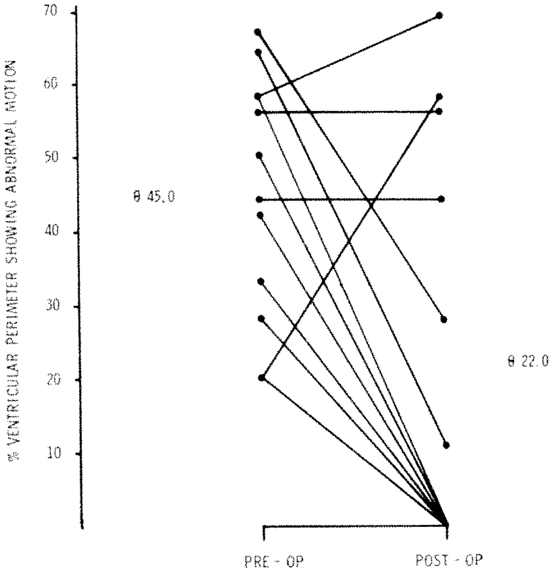

Fig. 6 *Quantitative changes in segmental wall motion after combined aortic valve replacement and coronary artery bypass grafting.*

ficant decrease in left ventricular end-diastolic pressure from a mean of 13 mmHg to a mean of 6 mmHg (Fig. 5) ($t=3{\cdot}91$, $P<0{\cdot}0015$).

Analysis of segmental wall motion in these 19 patients before operation showed localised abnormalities of wall motion in nine patients (47%), generalised hypokinesia in three patients (16%), and a normal pattern of contraction in seven patients (37%). After operation localised abnormalities of wall motion improved in six of the nine patients (67%) (Table 4), deteriorated in one patient, and were unchanged in two patients. The two patients showing no change in wall motion abnormalities had both had a myocardial infarction before operation. The one patient showing deterioration had sustained perioperative infarction. Of the three patients with generalised hypokinesia preoperatively, two subsequently improved, and one showed further deterioration; in the latter case the deterioration was associated with occlusion of a graft to the affected segment. The seven patients with a normal pattern of contraction preoperatively were found to be unchanged at reinvestigation.

Table 4 *Changes in left ventricular contraction pattern in 19 patients after aortic valve replacement and coronary artery bypass grafting*

Contraction pattern before operation	*Improved*	*Unchanged*	*Deteriorated*
Normal (7)	0	7	0
Localised wall motion abnormalities (9)	6	2	1
Generalised hypokinesia (3)	2	0	1

Quantitative changes in segmental wall motion in the 12 patients with abnormal motion before operation (localised or generalised) are shown in Fig. 6. The percentage of the ventricular perimeter showing abnormal motion decreased after operation from a mean of 45 per cent to a mean of 22 per cent (t= 2·67, P<0·015). Normal wall motion was restored in six patients (50%). Improvement in wall motion with residual abnormalities occurred in two patients (17%), remained unchanged in two patients (17%), and deteriorated in two patients (17%).

Fig. 7 a-c show examples of pre- and post-operative analysis of segmental wall motion. Fig. 7a illustrates a patient with predominantly inferior hypokinesia before operation which returned to normal apart from a minor abnormality at the site of the apical vent after valve replacement and a graft to the right coronary artery. Ejection fraction increased from 0·52 to 0·71. Fig. 7b illustrates a patient with generalised hypokinesia affecting most of the anterior and the inferior surface. After operation the contraction pattern returned to within normal limits and the ejection fraction increased from 0·33 to 0·61. This patient had a graft to the anterior descending artery. The right coronary artery was also severely diseased but was a non-dominant vessel and was, therefore, not grafted. Fig. 7c illustrates a patient with anterior hypokinesia before operation who sustained anterior and inferior perioperative infarction with subsequent extension of anterior hypokinesia and the appearance of slight inferior hypokinesia. Ejection fraction decreased from 0·57 to 0·50. A single graft was inserted into the anterior descending artery and this was found to be patent, with good distal run-off. The right coronary artery and circumflex artery showed only minor irregularities.

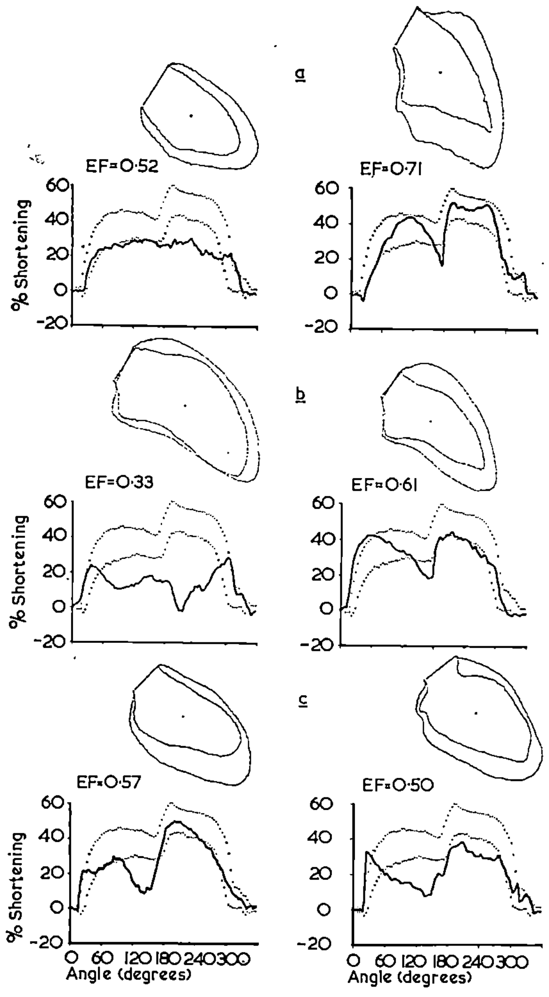

Fig. 7 a-c *Computerised radial analysis of segmental wall motion before (left hand panel) and after (right hand panel) operation in three patients. Percentage shortening of radials (vertical axis) is plotted against angle in degrees around the ventricular perimeter (horizontal axis). The dotted lines indicate the normal values ±2 standard deviations in a group of 30 normal patients. EF, ejection fraction. (See text for details.)*

Discussion

Most patients in this series derived considerable benefit from combined homograft replacement of the aortic valve and coronary artery bypass grafting, both in terms of relief of symptoms and in improvement in the quality of life. Actuarial analysis of survival has shown that the early and late mortality of the combined procedure is not significantly different from that we have reported for patients undergoing isolated, elective homograft replacement of the aortic valve (Thompson *et al.,* 1977). However, the number of patients in the combined series is small and the duration of follow-up is shorter in this group and further evaluation is required. Though many studies (Loop *et al.,* 1972; Oury *et al.,* 1972; Anderson *et al.,* 1973; Cooley *et al.,* 1973; Berndt *et al.,* 1974; Berger *et al.,* 1975; Callard *et al.,* 1976) have shown that aortic valve replacement can be safely combined with coronary artery bypass grafting, other authors have reported an increased operative and late mortality with a high incidence of postoperative myocardial infarction (Loop *et al.,* 1977).

Although perioperative myocardial damage in the present series was assessed using electrocardiographic criteria alone, the incidence of infarction was similar to that we have reported for coronary artery bypass grafting alone (Yacoub *et al.,* 1976). No late infarctions have occurred to the present time. Unfortunately there is no comparable prospective series in which the results of isolated aortic valve replacement can be evaluated, in terms of mortality and incidence of myocardial infarction, in patients known to have coronary artery disease. Our experience with such patients is limited to seven patients who, though known to have coronary artery disease, underwent isolated aortic valve replacement before we started to perform the combined procedure. Two of these patients had a perioperative infarction and five of the seven patients have since died, the cause of death being left ventricular failure consequent on myocardial infarction in each case (Thompson *et al.,* 1979b).

Although adequate myocardial protection is of great importance, there have been no significant differences in the extent of myocardial injury in reported series using a variety of current techniques (Sapsford *et al.,* 1974; Karp and Lell, 1976). Similarly the sequence of valve replacement and bypass grafting does not appear significantly to influence the extent of myocardial damage. Rossiter *et al.* (1974) reported a higher incidence of myocardial damage after coronary perfusion, which may have been the result of injury to the coronary ostia during cannulation (Heilbrunn and Zimmerman, 1965; Ramsey *et al.,* 1967) or inadequate subendocardial perfusion in the fibrillating, hypertrophied ventricle (Hottenrott *et al.,* 1973). However, the incidence of perioperative infarction in their series was not significantly different from that in a group of patients using hypothermia alone. It has been our practice to combine continuous coronary perfusion of a beating heart with moderate degrees of hypothermia.

The cause of poor left ventricular function in patients with aortic stenosis remains uncertain. In these patients, in addition to the increased myocardial oxygen demand, myocardial perfusion may be greatly reduced even in the absence of coronary artery disease (Fallen *et al.,* 1967). A prolonged systolic ejection time and tachycardia reduce the time available for diastolic coronary filling, particularly in the subendocardial regions (Vincent *et al.,* 1974). Other factors limiting myocardial blood flow include increased systolic left ventricular wall tension (Rodbard *et al.,* 1964), low mean aortic pressure, and abnormal flow patterns in the aortic root (Bellhouse and Bellhouse, 1969). Long-standing relative coronary insufficiency may lead to progressive changes in myocardial architecture and in the myocardial ultrastructure (Maron *et al.,* 1975; Naeye and Liedtke, 1976; Schwarz *et al.,* 1978). Additional coronary artery disease may increase the severity of these changes and lead to further deterioration in left ventricular function and myocardial infarction. Recent work has suggested that though increased afterload contributes to the development of impaired left ventricular function it is not a major determinant of myocardial performance (Liedtke *et al.,* 1976). Similarly, we found no correlation between severity of aortic stenosis and extent of depression of left ventricular function (Thompson *et al.,* 1979b). Changes in left ventricular function after valve replacement are therefore unlikely to be related simply to changes in left ventricular afterload.

Improvement in left ventricular function, as judged by changes in segmental wall motion and ejection fraction, occurred in the majority of patients reinvestigated in this series, and appeared to be closely related to graft patency and the presence or absence of previous infarction. It is not possible, however, to determine the extent to which improvement in left ventricular function could be expected with valve replacement alone, as opposed to the combined procedure. Limited data (Thompson *et al.,* 1979b) suggest that short-term improvement in left ventricular function may occur after valve replacement in patients with coronary artery disease in the absence of additional coronary bypass grafting. However, subsequent follow-up of such patients indicates that progressive coronary artery disease results in further deterioration in left ventricular function usually consequent on myocardial infarction.

The good clinical results, with low early and late mortality of combined valve replacement and coronary artery bypass grafting, have encouraged us to believe that this is a valuable procedure which in the longer term may favourably influence the prognosis and reduce late myocardial infarction in patients with aortic stenosis and coronary heart disease.

We wish to thank Ms Margaret Rehahn and Dr S. C. Rogers for performing the statistical analysis of our data and for their advice on statistical methods.

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Thallium-201 myocardial imaging in assessment of results of aortocoronary bypass surgery

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SUMMARY Thirty-six patients were assessed by thallium-201 myocardial imaging before and after aortocoronary bypass operations and the results were compared with evaluation based on symptomatic assessment, exercise testing, and electrocardiography.

After operation, the majority of patients were free from symptoms or symptomatically improved with increased exercise duration. Perioperative myocardial damage was shown in eight patients and myocardial ischaemia in 15 patients when assessed by thallium imaging during exercise. Thallium imaging proved more sensitive than electrocardiography in the demonstration of perioperative infarction and in the detection of postoperative ischaemia. Exercise electrocardiography may be misleading after aortocoronary bypass operations.

Thallium imaging offers a simple, objective evaluation of the results of revascularisation procedures, throws light on the mechanisms of relief of angina by operation, and helps in the assessment of the patient whose progress is unsatisfactory after operation.

Aortocoronary bypass surgery has become an established treatment for symptomatic obstructive coronary artery disease which is refractory to medical treatment. After operation the majority of patients are free from symptoms or substantially improved, with increased exercise capacity and, in general, this is related to graft patency though the relation is imprecise; some patients show improvement in both symptoms and exercise performance after perioperative myocardial infarction (Di Luzio *et al.*, 1974) or when all the grafts are occluded (Benchimol *et al.*, 1976). The suggested mechanisms for relief of angina comprise: a placebo effect of operation, denervation of the ischaemic myocardial segment, perioperative infarction of the previously ischaemic segment, improvement of left ventricular function, and improvement of myocardial blood flow by a patent bypass graft (Mnayer *et al.*, 1977). Objective assessment of the effects of bypass surgery on regional myocardial perfusion would contribute to the investigation of these possible mechanisms for relief of angina and aid management of the patient whose progress after operation is unsatisfactory. Thallium-201 myocardial imaging has proved a sensitive technique for the study of myocardial perfusion and we report here our experience using this technique to assess patients before and after coronary artery bypass surgery and compare the results with those from evaluation based on symptomatic assessment, electrocardiography, and exercise testing.

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Patients and methods

Thirty-six patients were studied before and after elective aortocoronary bypass surgery for stable angina pectoris. The study sequence comprised: clinical assessment, resting electrocardiography, resting thallium-201 myocardial imaging, exercise testing, exercise electrocardiography, and exercise thallium-201 myocardial imaging. Studies were performed preoperatively, at the time of cardiac catheterisation, and four to six months postoperatively.

CLINICAL ASSESSMENT

Angina was graded by New York Heart Association (NYHA) criteria. Previous myocardial infarction was established on the basis of a documented history of infarction or of diagnostic changes on the resting electrocardiogram.

EXERCISE TESTING

Patients were exercised on a bicycle ergometer (Elema Schonander EM 369). A standardised exercise procedure was employed with an initial work load of 24·5 watts (150 kpm/min) for two minutes, increasing by 24·5 watts (150 kpm/min) every two minutes to the maximum tolerated work load. Beta-blocking drugs and other antianginal treatment were discontinued for 48 hours before testing and the patients were fasted for eight hours. During exercise nine electrocardiographic leads (I, II, III, aVR, aVL, aVF, V4, V5, and V6) were monitored continuously. The exercise electrocardiogram was considered to demonstrate ischaemia if, in a lead with an isoelectric ST segment and upright T wave at rest, there was ST segment depression of at least 100 μV, persisting for 0·08 second after the termination of the QRS complex, with a horizontal or downsloping ST segment, and present for at least three consecutive beats during exercise or the first three minutes of recovery. The exercise test was discontinued with the development of angina, ST segment depression of 300 μV or more, breathlessness, or exhaustion: a 'target' heart rate was not used. Exercise performance was documented in terms of total exercise duration using the standardised procedure and maximum heart rate achieved during exercise.

THALLIUM-201 MYOCARDIAL IMAGING

Myocardial imaging was performed at rest and after maximal exercise. On each occasion 1·5 mCi thallium-201, as thallous chloride (Philips Duphar DRN 8103) was given intravenously. The patient was fasted for eight hours before imaging. For the resting study imaging started 10 to 15 minutes after isotope injection; for the exercise study the isotope was administered during maximal exercise; exercise was continued at, or near, this level for a further one minute, and imaging started 10 minutes later. Imaging was completed within 30 minutes to reduce to a minimum the effects of redistribution of the isotope occurring after initial myocardial uptake. Three standard views of the myocardium were obtained, anterior, 45° left anterior oblique, and 90° left lateral, with additional views as indicated. The mercury *x*-ray emission (65 to 82 keV) from thallium-201 decay was imaged using a scintillation camera (General Electric Maxicamera), with a low-energy, high-resolution, converging collimator. Each image consited of 300 000 counts and these were computer processed to produce a semiquantitative, 15-colour display.

The normal left ventricular myocardial image shows relatively uniform isotope uptake throughout the myocardium. A defect is defined as a reduction of myocardial counts to below 75 per cent of the maximum myocardial counts on that image (Lenaers *et al.*, 1977). A defect on the resting images which is unchanged on subsequent exercise images represents infarction, while the appearance of a new defect on exercise images or a substantial increase in the extent of a defect previously shown at rest represents ischaemia.

CARDIAC CATHETERISATION AND CARDIAC SURGERY

Selective coronary arteriography with multiple views of both right and left coronary arteries was performed using the Judkins technique. A coronary arteriographic lesion was considered significant if the luminal diameter was reduced by 50 per cent or more. At operation an attempt was made to revascularise all vascular territories with greater than 50 per cent stenosis of the supplying artery shown at coronary arteriography. Grafts were not established to vessels supplying obviously infarcted myocardium or to vessels with severe distal disease or inadequate 'run-off'. Cardiopulmonary bypass was conducted by bubble oxygenator with moderate haemodilution at 32°C. Aortocoronary bypass grafts were constructed using reversed segments of autologous saphenous vein. The distal anastomoses were made with the heart arrested either by electrical ventricular fibrillation or by hypothermic cardioplegia. In a number of cases sequential grafts were anastomosed to adjacent arterial branches in the same vascular territory. Endarterectomy was performed at the site of the distal anastomosis if necessary. The proximal anastomoses to the aorta were completed with the heart beating and often after discontinuation of cardiopulmonary bypass. All patients in this series had bypass grafts alone, and none had resection of a left ventricular aneurysm.

POSTOPERATIVE ASSESSMENT

The patients were reassessed four to six months after operation in the same way as before operation. Perioperative myocardial infarction was established by the appearance of new Q waves on the resting electrocardiogram at that time.

Results

The clinical features, coronary arteriographic findings, bypass grafts constructed, exercise data, electrocardiographic observations, and results of thallium-201 myocardial imaging are shown in Tables 1a and 1b. Thirty-six patients (34 men and two women, average age 52 years) with stable angina pectoris had aortocoronary bypass graft operations. Four patients had single vessel disease, eight had double vessel disease, and 24 had triple vessel disease. One hundred and two vessels were grafted using 78 single grafts and 12 sequential grafts. Endarterectomy was necessary before grafting in 19 vessels.

Table 1a *Symptoms, exercise duration, coronary arteriography, and grafts*

Case no.	*Sex*	*Age (y)*	*Angina (NYHA)*		*Exercise duration (min)*		*Coronary stenosis ≥50%*	*Bypass grafts*
			Preop	*Postop*	*Preop*	*Postop*		
1	M	42	2	1	16	15·5	LAD Dg Cx R	LAD Dg R
2	M	59	2	1	10·5	12	LM LAD OM R	LAD Dg R
3	M	60	3	2	6	9	LAD Dg Cx R	LAD/Dg OM R
4	M	65	2	1	8	8	LAD OM R	LAD Dg R
5	M	50	3	1	5·75	11	LAD Dg Cx OM R	Dg R
6	M	56	3	1	6	12	LAD OM R	LAD/Dg OM R
7	M	50	4	1	8	12	LAD Cx OM	LAD/LAD Dg OM/OM
8	M	57	4	1	4	9·5	LAD Cx R	LAD Dg R
9	M	57	2	1	6	10·75	LM LAD Cx OM R	LAD OM R
10	M	53	2	1	8·75	9·5	LAD OM R	LAD R
11	M	54	3	2	8	9	LAD Cx	LAD OM
12	M	52	3	3	8	8	LAD Cx R	LAD OM R
13	M	46	3	1	6	10·75	LAD Cx R	LAD OM R/R
14	M	56	3	1	5	13	LAD OM R	LAD OM R
15	M	63	3	1	5·5	8·5	LAD Cx OM R	LAD OM R
16	M	44	2	1	13·75	16	LAD OM R	LAD OM R
17	M	53	3	1	6	9·5	LAD Dg OM R	LAD/Dg OM R
18	M	44	2	1	11·5	13	LAD Dg R	LAD OM R
19	M	59	3	1	8	11·75	LAD OM R	LAD OM R
20	M	43	2	1	11·25	14	LAD Dg OM R	LAD/Dg OM R
21	M	48	3	1	4	7·25	Dg Cx OM R	Dg/Dg OM R/R
22	M	41	2	1	10	11	LAD Cx	LAD OM
23	M	49	2	1	11	9·5	LAD R	LAD R
24	M	42	2	1	16	17·5	LAD	LAD
25	M	49	2	1	7	12	OM	LAD OM
26	M	60	2	1	8	10	LAD R	LAD
27	M	49	3	2	5·75	7·5	LAD Dg Cx OM R	LAD OM R
28	F	40	2	1	7·75	8	LAD	LAD
29	M	57	3	3	8·75	9	LAD Cx OM R	LAD/Dg OM
30	M	50	2	1	9·5	13	Dg OM R	LAD/Dg OM R
31	M	44	2	1	10	13·5	LAD	LAD R
32	M	60	3	1	4·5	8	LAD Cx OM R	LAD OM R
33	M	66	3	3	5·5	6	LAD Dg OM R	LAD
34	M	50	2	1	10	11·5	LAD R	LAD R
35	F	63	3	3	4	4	LAD Cx OM	LAD OM/OM
36	M	49	2	2	9·5	9	LAD Cx OM R	LAD OM R

Abbreviations: LM, left main coronary artery; LAD, left anterior descending coronary artery; Dg, major diagonal branches of LAD; Cx, left circumflex coronary artery; OM, obtuse marginal branches of Cx; R, right coronary artery; LAD/Dg, sequential graft.

SYMPTOMS

Before operation all patients had significant angina; 19 were NYHA grade 2, 16 were grade 3, and one was grade 4. After operation, 28 patients (78%) were free from symptoms, three (8%) were improved (grade 2), and five (14%) were unchanged, four with continuing severe angina (Table 1a).

EXERCISE TESTING

The results of pre- and postoperative exercise studies show that, for the group as a whole, mean exercise duration increased from 8·15 (±3·07) minutes before operation to 10·54 (±2·83) minutes after operation ($P < 0·001$). The maximum heart rate achieved increased from 136 (±21)/min before operation to 156 (±19)/min after operation ($P < 0·001$). Statistical analysis was by paired Student t test.

RESTING ELECTROCARDIOGRAPHY

Before operation 17 patients had electrocardiographic evidence of previous myocardial infarction. After operation two patients had new Q waves on the resting electrocardiogram while 16 had persistent T wave inversion in anterior or anterolateral chest leads not present before operation (Table 1b).

EXERCISE ELECTROCARDIOGRAPHY

Before operation 29 patients had ischaemic ST segment depression occurring during exercise in at least one lead of the electrocardiogram, and 26 of these developed angina during the exercise test. One additional patient developed left bundle-branch block with the onset of angina. Six patients had no electrocardiographic changes during exercise. After operation 13 patients had ischaemic ST segment depression during exercise but only four of these developed angina during the exercise test. In 10 of the 13 patients ST segment depression developed at a greater work load after operation than before (Table 1b).

RESTING THALLIUM-201 IMAGING: INFARCTION (Tables 1b and 2)

Before operation 14 patients had defects on resting thallium images which corresponded in location to

Table 1b *Localisation of ischaemia and infarction by electrocardiography and myocardial imaging*

	Rest studies (infarction)				*Exercise studies (ischaemia)*			
Case no.	*Preop ECG*	*Tl-201*	*Postop ECG*	*Tl-201*	*Preop ECG (max. ST depression) (mm)*	*Tl-201*	*Postop ECG (max. ST depression) (mm)*	*Tl-201*
1	INF	INF	T↓	—	2	AS INF	1	AL
2	—	—	T↓	—	3	AS AL	—	—
3	—	—	—	—	2	AL	3	AL
4	AS INF	AS INF	—	—	1	AS INF	—	AS
5	AS INF	AS AL INF	T↓	—	5	PL INF	1	—
6	INF	INF	T↓	—	1	AS INF	—	—
7	—	—	T↓	—	3	AL	1	AL
8	—	—	—	—	LBBB	AS INF	LBBB	—
9	—	—	T↓	AS*	3	AS INF	—	—
10	AS	AS	—	—	—	AS INF	—	—
11	AS	AS	T↓	AL	3	AS AL INF	1	AL
12	INF	—	—	—	3	PL INF	—	INF
13	—	—	—	—	3	PL	—	—
14	AS	AS	—	—	2	AS INF	2	—
15	AL INF	PL INF	T↓	—	1	PL INF	—	INF
16	INF	INF	—	—	1	AL PL INF	2	PL
17	AL INF	PL INF	—	—	3	INF	1	—
18	—	AS INF°	T↓	—	1	AS INF	—	—
19	AS	AS	—	—	—	—	—	—
20	—	—	—	—	2	AL PL	1	—
21	INF	INF	T↓	—	2	PL	—	—
22	—	—	—	—	—	INF	—	—
23	—	—	AL INF	AL INF	2	AL INF	—	INF
24	—	—	T↓	—	1	AS AL	—	—
25	—	—	T↓	—	1	PL INF	1	PL INF
26	—	—	—	—	—	INF	—	—
27	—	—	INF	PL	1	PL INF	3	INF
28	—	—	—	—	1	AS	—	—
29	AS	—	AS†	AL	1	AS INF	—	AS
30	INF	INF	—	—	1	INF	—	—
31	AS	—	—	—	1	AS AL	—	—
32	AS	AS PL	T↓	AS*	4	—	—	—
33	—	—	T↓	—	1	AL PL	1	AS AL
34	—	PL	—	—	—	AL INF	—	—
35	—	—	T↓	AS	3	AS AL	2	AS AL
36	—	—	T↓	AS	—	AS INF	—	INF

AS, anteroseptal, AL, anterolateral; PL, posterolateral; INF, inferior/posterior; *, patchy necrosis; °, severe ischaemia; †, ST segment elevation after operation; T↓, T wave inversion in anterior or anterolateral leads after operation; LBBB, left bundle-branch block.

Table 2 *Thallium-201 myocardial imaging—infarction*

Electrocardiogram		*No. of patients*	*Thallium-201 imaging*	
			Defect (infarction)	*Normal*
Preoperative	Q waves	17	14	3
	Normal	19	1	18
Postoperative	New Q waves	2	2	0
	T wave inversion	16	5	11
	Unchanged	18	1	17

the electrocardiographic signs of previous infarction. In three patients with electrocardiographic evidence of infarction resting images were either normal or minimally abnormal. One patient had a posterolateral defect on thallium images without electrocardiographic evidence of infarction and another patient had anteroseptal and inferior defects on thallium images suggesting infarction but the resting images after operation were normal suggesting that the preoperative abnormalities represented ischaemia rather than infarction.

After operation, thallium imaging suggested new myocardial infarction in eight patients. Two had new Q waves on resting electrocardiograms. One, with previous anteroseptal infarction, had conspicuous ST segment elevation in anteroseptal leads immediately after operation but there was no increase in the extent of Q waves on the resting electrocardiogram subsequently. Five had T wave inversion in anterior leads; the thallium images in two of these patients suggested patchy anteroseptal necrosis.

EXERCISE THALLIUM-201 IMAGING: ISCHAEMIA (Tables 1b and 3)

Before operation 34 patients had evidence of ischaemia on exercise thallium images: 28 of these developed ischaemic ST segment depression during exercise, one developed left bundle-branch block,

Table 3 *Thallium-201 myocardial imaging—ischaemia*

Electrocardiogram		*No. of patients*	*Thallium-201 imaging* *Defect (ischaemia)*	*Normal*
Preoperative	ST depression	29	28	1
	Non-specific	7	6	1
Postoperative	ST depression	13	9	4
	Non-specific	23	6	17

and five had no changes on exercise electrocardiography. One patient with gross ST segment depression had extensive infarction rendering interpretation of the exercise thallium images difficult and one patient had no evidence of ischaemia on either test.

After operation 15 patients had evidence of continuing ischaemia on thallium imaging though in the majority the extent of the abnormality was reduced. All eight patients with persistent postoperative angina were in this group. Nine of these patients had ST segment depression on electrocardiography during exercise. Twenty-one patients had no evidence of ischaemia on thallium imaging after operation; all were free from symptoms and none had chest pain during exercise, but four developed ST segment depression at heavy work loads. Repeat coronary arteriography was undertaken on three patients (cases 33, 35, and 36) who had continuing and intractable angina after operation. In one patient (case 33) extensive anterior ischaemia on postoperative exercise thallium imaging correctly predicted occlusion of his single left anterior descending coronary artery graft. In the second patient (case 35) postoperative thallium imaging showed anteroseptal ischaemia and a limited anterior infarct; left ventriculography after operation showed a new region of apical hypokinesia, the left anterior descending graft was occluded, and the sequential graft to the two circumflex branches was severely narrowed. In the third patient (case 36) postoperative thallium imaging showed infarction of the previously ischaemic anteroseptal region with severe inferior ischaemia; left ventriculography showed a new region of anterior hypokinesia and all three grafts were occluded.

Discussion

The symptomatic improvement which follows aortocoronary bypass graft operations is well established, with 70 to 80 per cent of survivors free from symptoms and approximately 90 per cent improved one to two years after operation (Dunkman *et al.*, 1974; Mundth and Austen, 1975). Evaluation of the functional result by maximal exercise testing and exercise electrocardiography gives results which are broadly in agreement with those from symptomatic assessment (Lapin *et al.*, 1973). Reported graft patency rates from several cardiac centres are similar, with 80 to 90 per cent of grafts patent six to 24 months after operation (Dunkman *et al.*, 1974). Good symptomatic results, improved exercise tolerance, and abolition of exercise-induced ST segment depression generally correlate with complete revascularisation and graft patency (Lapin *et al.*, 1973; Sheldon *et al.*, 1973), but this correlation is imprecise and similar results may be seen after perioperative myocardial infarction (Di Luzio *et al.*, 1974) or when all grafts are occluded (Block *et al.*, 1976; Benchimol *et al.*, 1976). Some patients who are free from symptoms after operation show 'ischaemic' ST segment depression without chest pain during exercise testing (Bartel *et al.*, 1973). This dissociation is only rarely seen before operation or on medical treatment and has led to the suggestion that some of the benefit of operation might be the result of a placebo effect or denervation of the ischaemic myocardial segment, as well as perioperative infarction of the previously ischaemic segment, improvement of left ventricular function, or improvement of myocardial blood flow by a patent bypass graft (Mnayer *et al.*, 1977).

Studies of left ventricular function at rest have given variable results, with improvement or worsening of overall or segmental function, often unrelated to graft patency (Chatterjee *et al.*, 1973; Hammermeister *et al.*, 1974; Shepherd *et al.*, 1974). Improved left ventricular function during exercise may be seen in patients with good preoperative left ventricular function and patent grafts (Barry *et al.*, 1976). Studies of left ventricular function and graft patency carry a potential risk, and it is probably no longer justifiable to undertake these routinely on patients who are free from symptoms after operation (Bristow *et al.*, 1977); in addition graft patency *per se* does not establish the extent of myocardial revascularisation. An objective assessment of myocardial perfusion is needed to investigate the results of operation.

Radioisotope techniques have been widely applied to the study of overall and regional coronary blood flow but studies on the results of coronary artery bypass operations have been limited. Xenon infusion provides a quantitative measure of regional myocardial perfusion and after successful grafting substantial increases of flow have been shown distal to the patent graft (Kreulen *et al.*, 1974; Korbuly *et al.,* 1975). A limited number of non-invasive studies, using the monovalent cations to provide a qualitative measure of regional myocardial perfusion, have shown improved perfusion associated with patent bypass grafts and persistent perfusion abnormalities related to ungrafted vessels, perioperative myocardial infarction, or occluded grafts. These studies have used potassium-43 (Zaret *et al.,* 1974), rubidium-84 (Knoebel *et al.,* 1974), rubidium-81 (Lurie *et al.,* 1976), and thallium-201 (Ritchie *et al.,* 1977a). Thallium-201 has become the radioisotope of choice for the non-invasive evaluation of myocardial perfusion. This has provided a highly sensitive technique for the detection of coronary artery disease, and comparison of rest and exercise myocardial images distinguishes ischaemia from infarction (Bailey *et al.,* 1977; Ritchie *et al.,* 1977b; Botvinick *et al.,* 1978). Myocardial uptake of thallium-201 correlates closely with regional myocardial perfusion determined independently using microspheres (Strauss *et al.,* 1975) and the technique has proved reproducible (McLaughlin *et al.,* 1977).

In this series the symptomatic results of operation were good with 78 per cent of patients free from symptoms and 86 per cent improved. Maximum heart rate achieved and duration of exercise were increased in the majority of patients. Evidence of perioperative myocardial infarction was found on thallium imaging in eight patients. In two of these the appearances suggested patchy anteroseptal necrosis with otherwise greatly improved perfusion. Myocardial necrosis may result from sudden reperfusion of a previously severely ischaemic region in patients in whom graft patency is later proven (Bulkley and Hutchins, 1977), and this is a possible mechanism in these cases. In the other six patients the thallium images suggested transmural infarction: two had new Q waves, one had transient ST segment elevation after operation, with no increase in the extent of Q waves subsequently, and three had T wave inversion in anterior leads. The limitations of standard electrocardiographic criteria for the detection of perioperative myocardial necrosis compared with measurement of isoenzyme release and pyrophosphate imaging have been previously recognised (Platt *et al.,* 1976; Klausner *et al.,* 1977). Thallium imaging provides a simple technique for the demonstration of significant perioperative necrosis. The overall incidence of necrosis in this study was 8/36 (22·2%). Persistent T wave inversion in anterior or anterolateral leads is commonly observed after operation; in the 16 patients in whom these changes were observed in this series, they had no consistent significance in terms of regional myocardial perfusion as judged by thallium imaging. It is possible that minor myocardial damage below the resolution of the thallium imaging technique may be responsible for these electrocardiographic changes; however, the otherwise excellent results seen in the majority of these patients and the common occurrence of these changes after other heart operations not involving coronary artery bypass grafting suggest that these changes probably do not represent significant myocardial damage.

On the results of thallium imaging after operation the patients may be divided into three groups (Table 4). Group 1 comprises 21 patients, all free from symptoms, with no evidence of ischaemia on thallium imaging after operation; 18 had improvement in exercise duration after operation, and in 11 out of 15 ST segment depression was no longer seen during exercise. These results suggest patent grafts and complete revascularisation. The two patients with patchy anteroseptal necrosis are included in this group. Group 2 comprises nine patients with evidence of ischaemia on thallium imaging after operation; six were free from symptoms, five had improved exercise duration, and in three out of nine ST segment depression was no longer seen after exercise, the remaining six continuing to show ST segment depression. These results suggest inadequate revascularisation or occluded grafts. Restudy has been undertaken on one patient in this group in whom ischaemia on

Table 4 *Thallium-201 myocardial imaging after operation*

Group	*Thallium-201 imaging*	*Number of patients*	*Angina (NYHA)*			*Exercise duration (min)*			*Resting ECG New Q waves*	*T inversion*	*Exercise ECG ST depression*
			1	*2*	*3*	+	=	–			
1	No ischaemia Complete revascularisation	21	21	0	0	18	3	0	0	8	4
2	Continuing ischaemia Partial revascularisation	9	6	1	2	5	4	0	0	5	6
3	Perioperative infarction and continuing ischaemia	6	1	3	2	2	3	1	2	3	3

Exercise duration: +, increased by 1 minute or more; =, unchanged; –, decreased by 1 minute or more (compared with preoperative).

thallium imaging after operation correctly predicted graft occlusion. Group 3 comprises six patients with perioperative myocardial infarction. In all, there was also evidence of ischaemia after operation; five of these patients still had angina, with little change in exercise tolerance, and three out of five continued to develop ST segment depression on exercise electrocardiography. Two patients in this group have been restudied: in each case left ventriculography showed a new region of hypokinesia corresponding to the infarcted myocardial segment, and the unchanged pattern of ischaemia in other myocardial segments was associated with graft occlusion.

Before operation, ST segment depression and the development of angina during exercise were closely related; however, after operation, 13 patients developed ST segment depression but only four of these developed angina during the exercise test. Nine of the 13 patients had definite evidence of ischaemia on thallium imaging though this was usually considerably reduced in extent compared with before operation. Four patients had continuing ST segment depression during exercise without evidence of ischaemia on thallium imaging, but in three of these there was evidence of previous infarction which may alter repolarisation during exercise.

This series does not represent a cross-section of our experience of coronary artery surgery during this period and is weighted by those patients whose progress after operation was complicated by persistence or recurrence of angina. It is not our policy to undertake reinvestigation by cardiac catheterisation in the absence of symptoms or if the preoperative or intraoperative assessment of left ventricular function and coronary anatomy suggest that a further operation would not be justified if graft occlusion were shown.

Thallium-201 myocardial imaging provides a simple, non-invasive, and objective assessment of regional myocardial perfusion after aortocoronary bypass operations and gives more information than symptoms, exercise testing, or electrocardiography. The technique elucidates the mechanisms of relief of angina by operation, helps in the management of the patient showing unsatisfactory progress after operation, and should prove useful in longer-term follow-up studies.

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British Heart Journal, 1979, **42**, 463–470

Multilevel block in the atrioventricular node during atrial tachycardia and flutter alternating with Wenckebach phenomenon

R. SLAMA, J. F. LECLERCQ, M. ROSENGARTEN, PH. COUMEL, AND Y. BOUVRAIN

From the Clinique Cardiologique, Hôpital Lariboisière, Paris, France

SUMMARY The electrocardiograms of 100 patients with rapid and regular PP intervals during atrial arrhythmias (because of atrial tachycardia or flutter, or pacing) were examined for periods of irregular atrioventricular conduction. This irregular conduction corresponds to an alternating Wenckebach phenomenon, of a type that can be determined from simple rules. The different types of conduction encountered in different patients and the changes seen in the same patient suggest that the atrioventricular node functions physiologically with 3 levels of sequential block. The different prevalence of the 2 types of alternating Wenckebach block may reflect functional differences at the level of the atrioventricular node.

The mechanism of atrioventricular conduction in atrial tachycardia and flutter is unclear. 2:1 or 4:1 conduction is most commonly seen and these ratios are the easiest to understand. However, conduction is often irregular and among the theories postulated to explain this behaviour is alternating Wenckebach phenomenon (Myerburg *et al.*, 1963; Amat-y-Leon *et al.*, 1975; Guerot *et al.*, 1975; Kosowsky *et al.*, 1976), but little has been published on how to determine the type of conduction from an individual tracing.

We propose a model based on 2 or 3 levels of atrioventricular nodal block, and detail a method to help identify the type of conduction from an individual tracing. Data for the study come from tracings recorded during rapid atrial tachycardia or atrial flutter, or during rapid atrial stimulation continued after reversion of the tachycardia or flutter.

Subjects and methods

We studied 100 patients with atrial tachycardia or flutter and an absolutely regular PP interval. This was done in the following manner:

(a) The atrial cycle length was measured exactly.

(b) The number of ventricular cycles required to make up an exact number of atrial cycles was determined. Starting with a relatively long RR interval, the RR intervals were then added until the total was equal to an exact marked multiple of atrial cycle length, giving a conduction ratio of x ventricular cycles for n atrial cycles.

(c) Special attention was given to changes in the conduction ratio on strips taken from the same patient, especially when the ratio was other than 4:1 or 2:1.

(d) The tracings were reviewed after treatment with digitalis or amiodarone as these often modified conduction and helped to find the type of block.

(e) Endocavitary studies were performed in the last 20 patients in order to define the level of conduction block.

(f) In those patients whose arrhythmia was successfully treated by atrial stimulation, with restoration to sinus rhythm, the atrioventricular conduction ratio that occurred before conversion was reproduced by incremental atrial pacing.

Results

TYPE A, ALTERNATING WENCKEBACH PHENOMENON

When the atrioventricular conduction ratio varied between 2:1 and 4:1 as often seen during drug therapy, the ventricular rhythm was irregular. With conduction ratios of 6:2, 8:3, or 10:4, the

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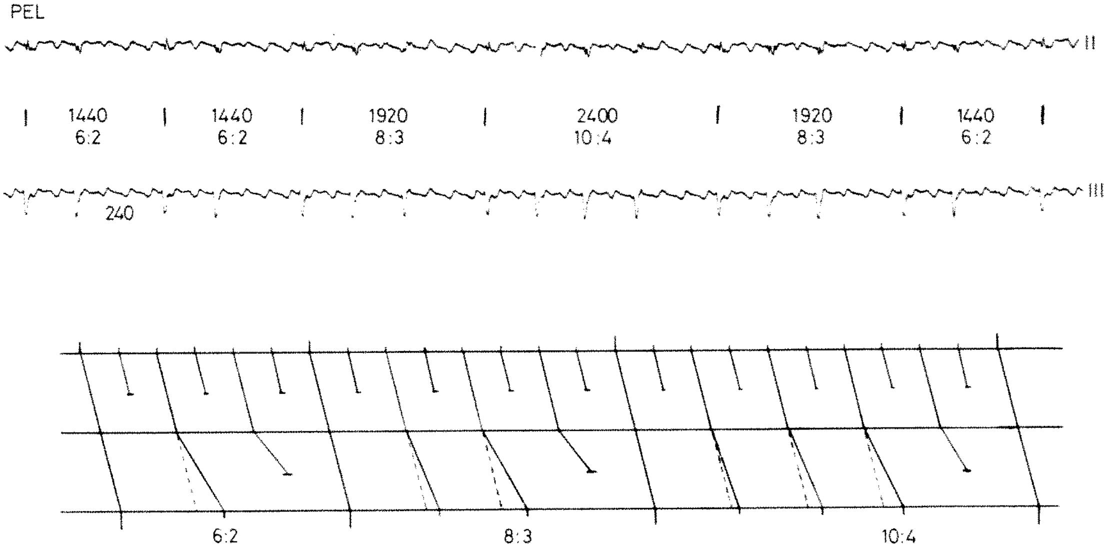

Fig. 1 *Type A alternating Wenckebach phenomenon* ($x=n)/(2-1$)*. The number of atrial cycles* (n) *corresponding to an exact number of ventricular cycles* (x) *is always even. The variability of the Wenckebach phenomenon in the second zone results in 3 ratios of* n/x *(6:2, 8:3, 10:4).*

stable conduction ratios with variable RR intervals were often modified by periods of varying conduction. This type of conduction can be represented by the following equation:

$$x = n/2 - 1 \text{ or } x = \left(\frac{n-2}{2}\right) \qquad \ldots.(1)$$

This type of conduction is well seen in Fig. 1 and corresponds to type A alternating Wenckebach phenomenon (Kosowsky *et al.*, 1976); it was seen in 75 per cent of our patients. It is due to block at two levels, the first showing 2:1 block, producing ($x=n/2$) and the second, the Wenckebach phenomenon, producing ($x=n)/(2-1$). If this latter Wenckebach phenomenon has a 3:2 ratio, the overall conduction ratio will be 6/2; if the phenomenon has a 4:3 ratio the overall conduction will be 8:3. It can be seen that it is easiest to derive this relation by starting from a long RR interval as this corresponds to the impulse blocked in the zone in which the Wenckebach phenomenon occurs.

Sometimes the relation between x and n is not exact because the sum of x ventricular cycles is slightly more than the sum of $n/2-1$ atrial cycles. The exact relation is seen in the sequence displayed in Fig. 2, where the sum of x ventricular cycles is slightly smaller than expected. This probably represents slowed atrioventricular conduction of the atrial impulse following the Wenckebach period, resulting from concealed conduction of the previously blocked atrial impulse, a phenomenon well known to occur in the atrioventricular node (Langendorf and Pick, 1966). In keeping with this is the finding that the delay seen in the first sequence is exactly compensated by the reduction in the sum of the RR intervals in the subsequent sequence.

TYPE B, ALTERNATING WENCKEBACH PHENOMENON

Another conduction pattern that may occur (Kosowsky *et al.*, 1976) is usually represented by:

$$x = \frac{n-1}{2} \qquad \ldots.(2)$$

In such cases conduction tends to be quite variable and ratios of 5:2, 7:3, and 9:4 may be encountered on the same recording. This model is the inverse of the former and the first level of block is the result of the Wenckebach phenomenon ($n-1$), with 2:1 block, $x=(n-1)/2$, at the next level.

Exact 3:1 block is rare and represents alternating Wenckebach phenomenon type B with 3:2 conduction at the second level (Slama *et al.*, 1978). 3:1 conduction is rarely stable and tends to alternate with 5:2 and 7:3 sequences. This second equation only applies to sequences with an odd number of atrial cycles, and applies to half the cases of two-level block in which the Wenckebach phenomenon occurs proximally and 2:1 block distally (Fig. 3). When there is an even number of atrial cycles that encounter this proximal level of Wenckebach block, that impulse conducted after the one that is blocked at the proximal level is, of course, blocked at the distal level. As a result the exact relation between n and x is only seen after two or more Wenckebach periods that is, after the first Wenckebach phenomenon with an even number of atrial impulses, the relation is only seen after a second period of Wenckebach phenomenon comprising an even number of atrial impulses (Fig. 4). As a result, during long recordings, it may be difficult to analyse the relation until one finds a few simple sequences that reveal a type B pattern. This mode of type B conduction can be expressed by the equation:

$$x = (n - y)/2 \qquad \ldots.(3)$$

where x is the number of ventricular cycles, n the number of atrial cycles, and y the number of Wenckebach periods.

Rules for atrioventricular conduction during atrial tachycardia or flutter are as follows:

(1) Type A alternating Wenckebach phenomenon implies a conduction ratio of $x = n/(2 - 1)$.

(2) Type B alternating Wenckebach phenomenon indicates a conduction ratio of $x = (n - 1)/2$.

(3) Type B alternating Wenckebach phenomenon with an even number of atrial cycles, or a type A alternating Wenckebach phenomenon with concealed conduction, can be represented by a conduction ratio of $x = (n - y)/2$.

The type of alternating Wenckebach phenomenon is usually constant when the patient's condition is stable. Under the influence of various stimuli, however, the type of conduction can change: this may be produced by changes in vagal or sympathetic tone associated with, for example, respiratory variations. Drugs like digitalis have a major effect on atrioventricular conduction and tend to slow it. The usual effect of such drugs is to alter 2:1 conduction to an alternating Wenckebach phenomenon by introducing a second level of block. This usually results in type A alternating Wenckebach phenomenon, though sometimes digitalis transforms type B alternating Wenckebach phenomenon into type A (Fig. 5).

Because 4:1 is the maximum conduction ratio with two levels of block, a ratio greater than 4:1 implies a third level of block. These 'slow' flutters are found in patients whose atrioventricular nodal function was previously impaired, as might have been seen when they were in sinus rhythm, or after larger doses of drugs like digitalis or amiodarone. In our 8 cases the conduction patterns fits a model

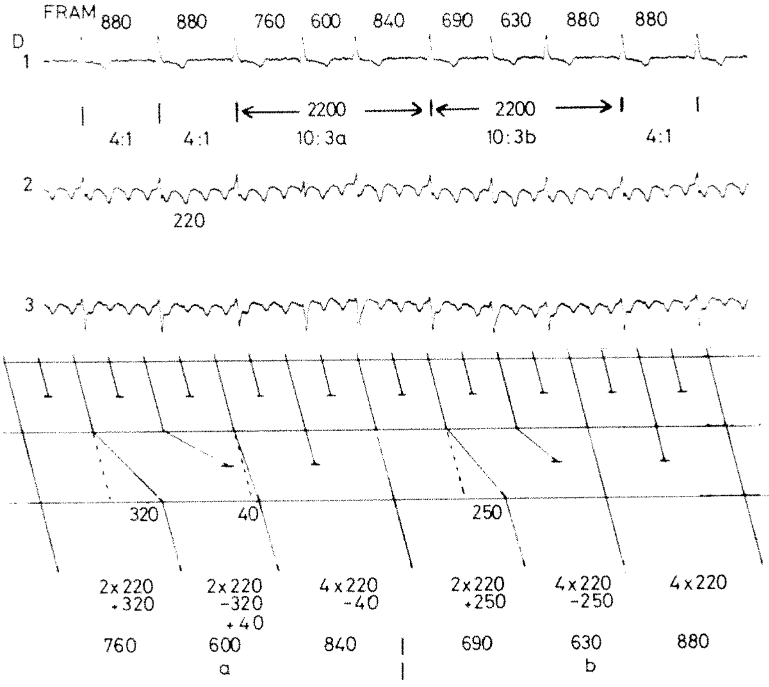

Fig. 2 *Type A alternating Wenckebach phenomenon with concealed conduction. During stable 4:1 conduction there are 10:3 sequences. The last 10:3 sequence* (b) *is divided exactly into a 6:2 and a 4:1 sequence. The first 10:3 sequence* (a) *is probably also divided this way, with a concealed atrial conduction between the 6:2 and 4:1 sequences (diagram). Note that the first RR interval of 760 ms* (a) *is longer than that in which it is 690 ms.*

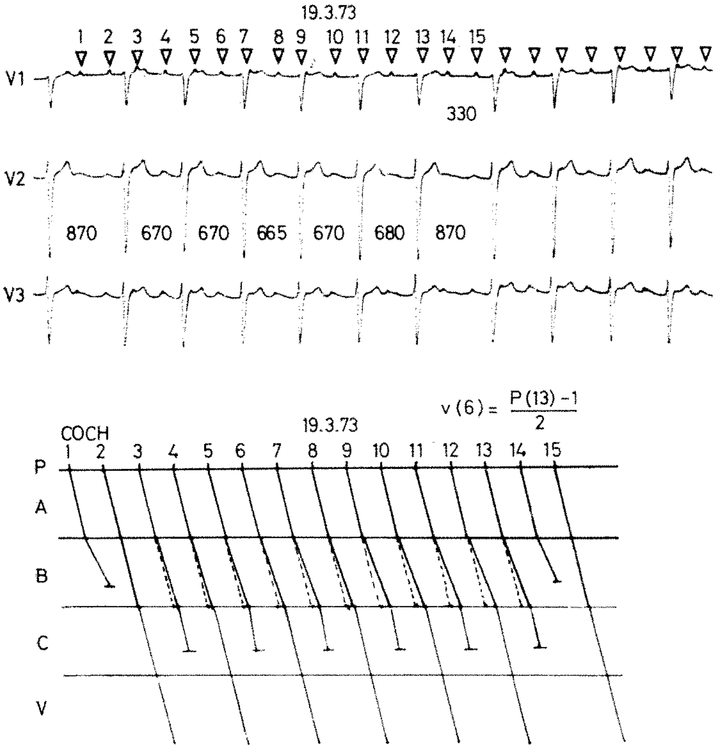

Fig. 3 *Type B alternating Wenckebach phenomenon. The conduction ratio of 13 :6 is explained by a 13 :12 Wenckebach phenomenon followed by a 2 :1 block.*

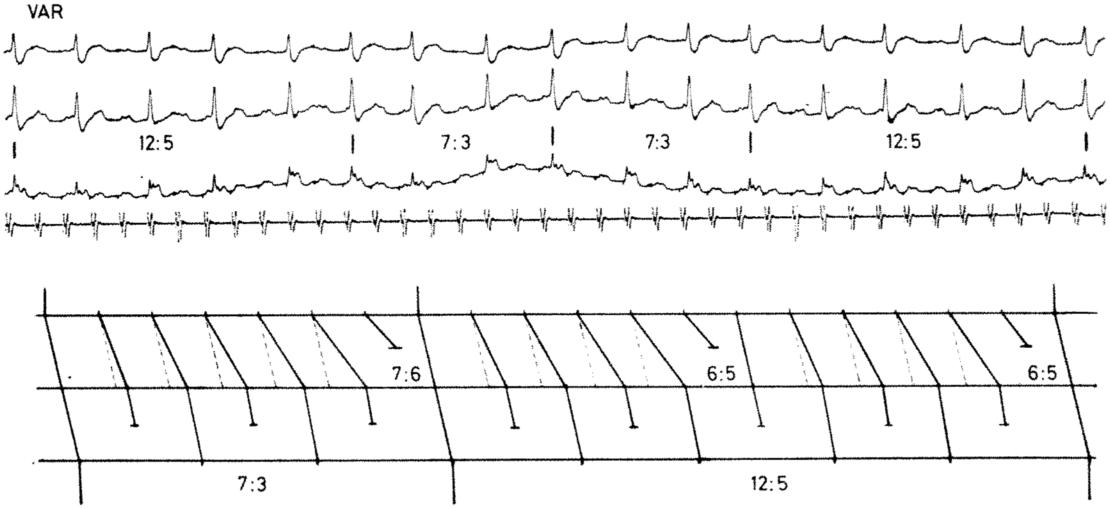

Fig. 4 *Type B alternating Wenckebach phenomenon recorded during atrial pacing. The first level of block is 7 :6 or 6 :5 Wenckebach phenomenon. A 7 :6 Wenckebach phenomenon gives a 7 :3 ratio. With a 6 :5 Wenckebach phenomenon the sixth atrial impulse is blocked by the zone of 2 :1 block and the following second 6 :5 Wenckebach phenomenon gives an overall 12 :5 ratio.*

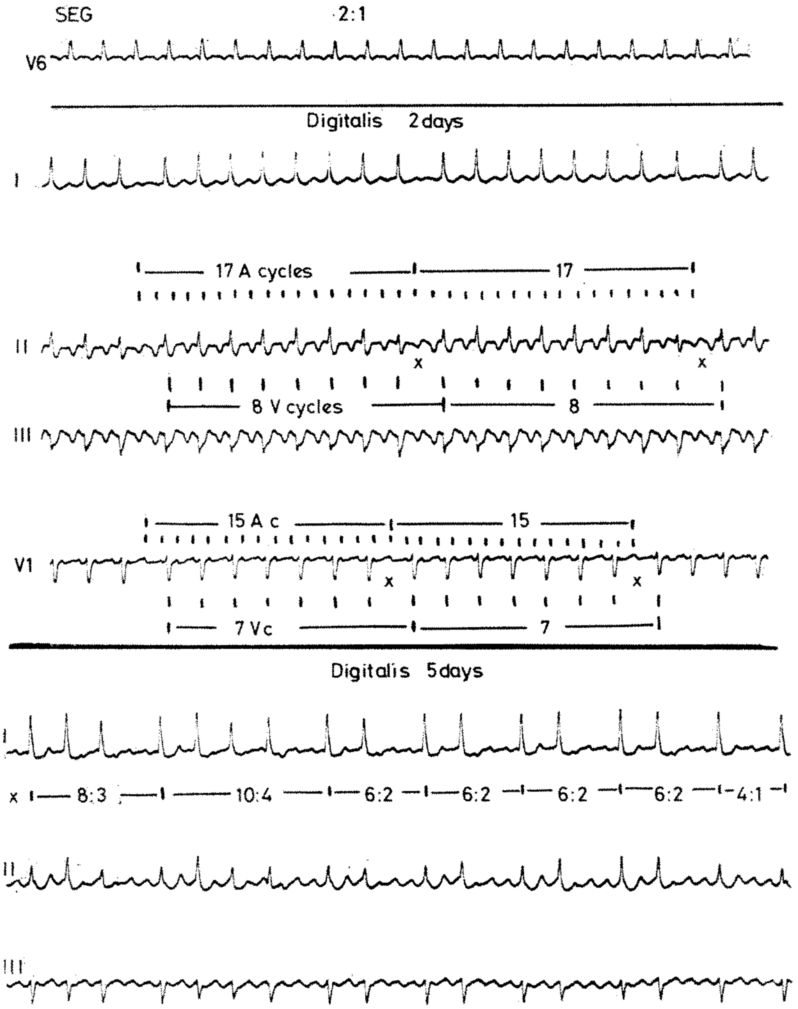

Fig. 5 *The effect of digitalis therapy in a case of atrial flutter with 2:1 atrioventricular conduction. After 2 days the conduction becomes a type B alternating Wenckebach phenomenon (17:8 or 15:7, where* $x = (n-1)/2$*). After 5 days the conduction becomes type A alternating Wenckebach phenomenon (6:2, 8:3, or 10:4, where* $x = n/2 - 1$*).*

with 2:1 block at the first level, a Wenckebach phenomenon at the second level, and a 2:1 block at the third (Fig. 6).

Our last 20 patients underwent right-sided intracardiac conduction studies. In each case the block was shown to be above the level of the bundle of His, as is usual in atrial flutter (Lau *et al.*, 1969; Dhingra *et al.*, 1973). In 11 cases it was possible to convert them to sinus rhythm by rapid rise atrial stimulation, after which the atrium was then paced at increasing rates. The following sequences of conduction changes were noted: (1) Wenckebach phenomenon; (2) 2:1 block; (3) alternating Wenckebach phenomenon; (4) 4:1 block; (5) block greater than 4:1.

If the first alternating Wenckebach phenomenon after 2:1 block was type A, this type of conduction was maintained until 4:1 block developed. On the other hand, if it was of type B, a change to type A might be seen before the development of 4:1 block (Fig. 7).

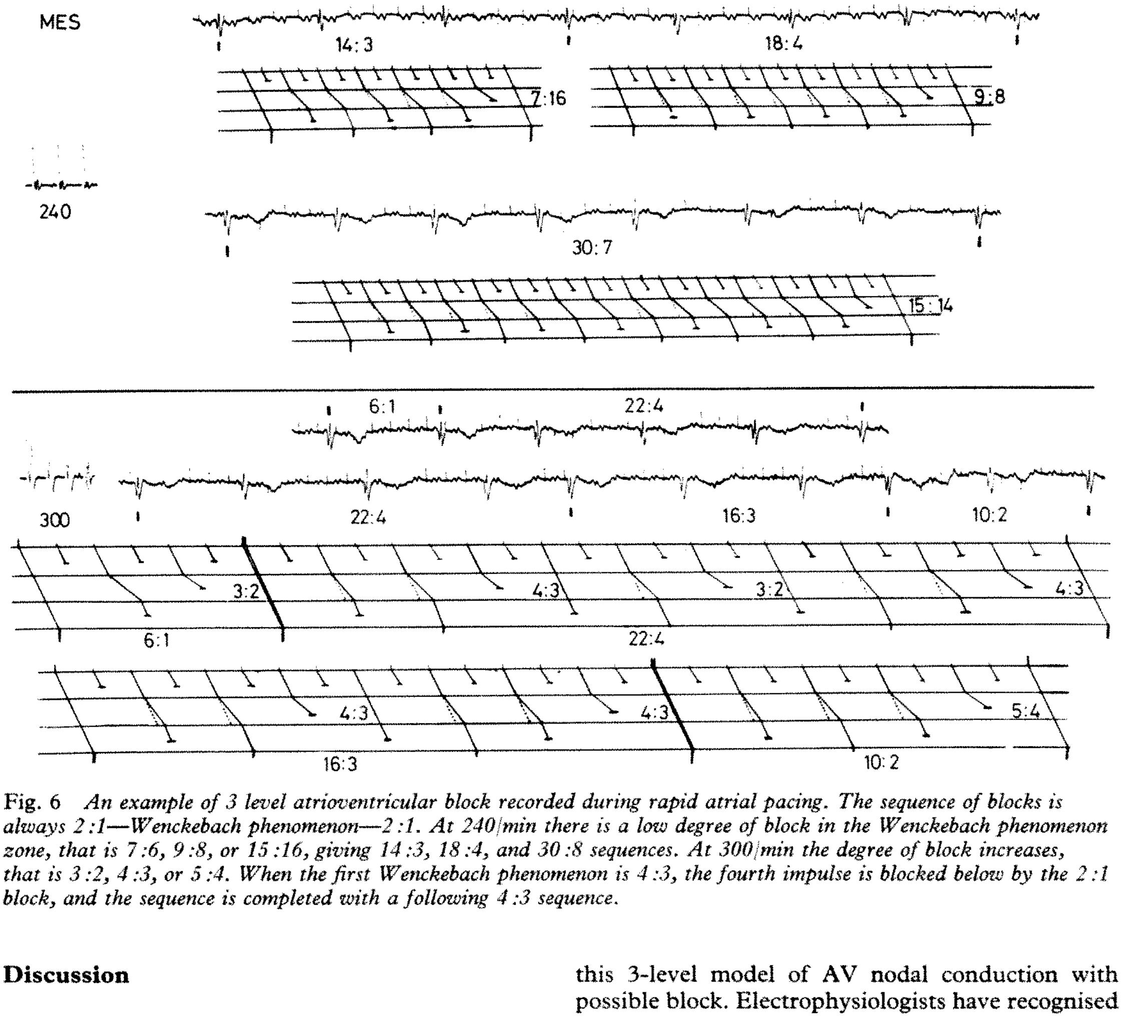

Fig. 6 *An example of 3 level atrioventricular block recorded during rapid atrial pacing. The sequence of blocks is always 2:1—Wenckebach phenomenon—2:1. At 240/min there is a low degree of block in the Wenckebach phenomenon zone, that is 7:6, 9:8, or 15:16, giving 14:3, 18:4, and 30:8 sequences. At 300/min the degree of block increases, that is 3:2, 4:3, or 5:4. When the first Wenckebach phenomenon is 4:3, the fourth impulse is blocked below by the 2:1 block, and the sequence is completed with a following 4:3 sequence.*

Discussion

Our findings of types A and B alternating Wenckebach phenomenon, the fact that they might change from one to the other, and the existence of block of greater degree than 4:1 suggest a model of the atrioventricular node with 3 possible levels at which block could occur. When analysis indicates the presence of 2 levels of block, 1 of these 3 levels will conduct in a 1:1 relation. Type A alternating Wenckebach phenomenon is more frequent (Kosowsky, 1976) than the other forms, and corresponds to a block in the first and second levels; type B corresponds to block in the lower 2 levels. Three-level block, with rare exceptions (Slama *et al.*, 1979), is represented by the model in Fig. 8. Here the first zone (A) shows 2:1 block, the second zone (B) Wenckebach phenomenon, and the third zone (C) 2:1 block.

There are a number of points that conform to this 3-level model of AV nodal conduction with possible block. Electrophysiologists have recognised 3 zones, AN, N, and NH (Mendez and Moe, 1966); the Wenckebach phenomenon is characteristically located in the N zone. This N zone corresponds to zone B of our model, and the AN and the NH zones respectively to A and C; 3:1 conduction has been recognised to occur very rarely (Lewis, 1912), and electrophysiological studies have shown this to be related to conduction disturbance at 2 successive levels (Watanabe and Dreifus, 1967). Further, the higher incidence of type A alternating Wenckebach phenomenon is understandable if one considers the sequence in which the atrial impulses penetrate the atrioventricular node. The impulse rate decreases in the first 2 levels, thus lowering the load on the most distal level and thereby allowing a higher percentage of impulses to be transmitted at that site (type B alternating Wenckebach phenomenon possibly corresponds to an anomaly in which

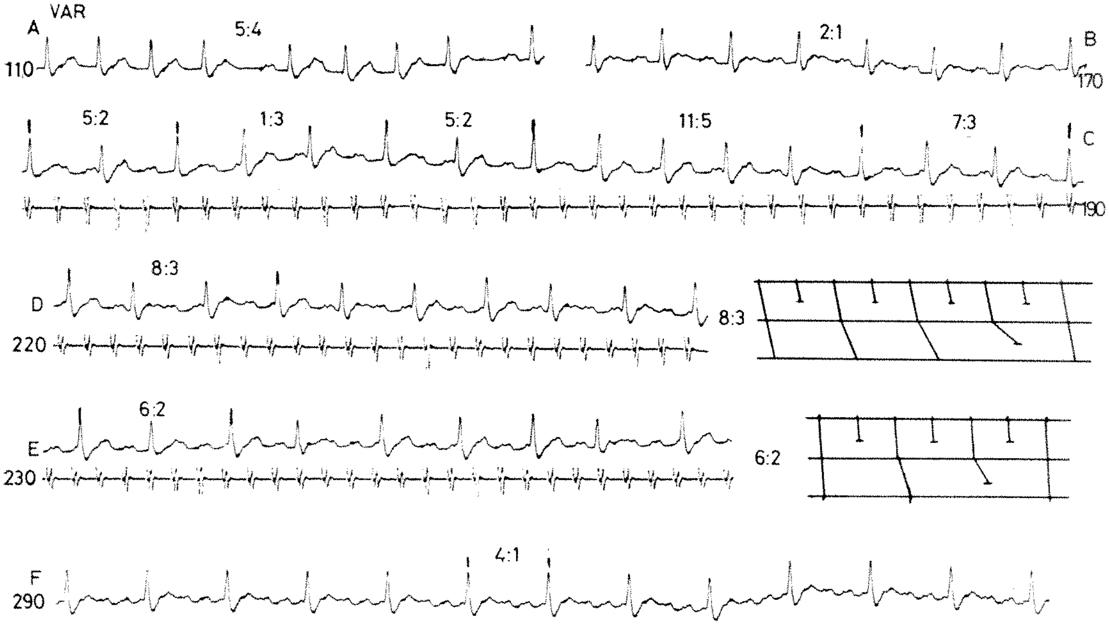

Fig. 7 *The atrioventricular response during a progressively increasing atrial pacing rate.* (A) *Wenckebach phenomenon at 110/min.* (B) *2:1 block at 170/min.* (C) *Type B alternating Wenckebach phenomenon at 190/min.* (D) *and* (E) *Type A alternating Wenckebach phenomenon at 220 and 230/min.* (F) *4:1 block at 290/min.*

there is a short-circuit of the A zone that may represent a condition analogous to the short PR syndrome with either partial bypass of AV nodal fibres or exceptionally good conduction at this zone, with a short refractory period). The alternating Wenckebach phenomenon appears to be a physiological reaction (Amat y Leon *et al.*, 1975; Castellanos *et al.*, 1977; Childers, 1977) and seems to correspond well with the anatomical model.

Finally, though we have seen type B alternating Wenckebach phenomenon converted to type A, we have never seen the opposite (an increased block in type A alternating Wenckebach phenomenon proceeds to 4:1 conduction without passing through type B block). The change from type B to type A alternating Wenckebach phenomenon implies the development of an additional conduction block in zone A. This reduces the number of impulses that reach zone C, and thereby encourages improved conduction in it; this may be analogous to the gap phenomenon. The increased block, whether induced by drugs or pacing, suggests an effect on the proximal part of the atrioventricular node.

We feel that the 3-level model of the AV node that we have proposed explains the majority of cases of alternating Wenckebach phenomenon conduction patterns and that it improves our understanding of the physiology of conduction of the AV node. Based on this model, we suggest simple rules that help determine the type of conduction block.

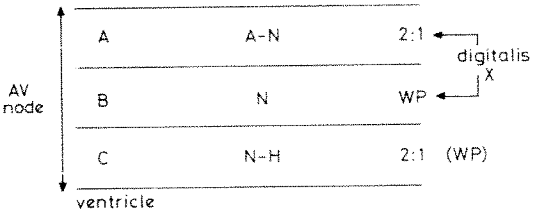

Fig. 8 *The model of the atrioventricular node, with 3 possible levels of conduction block.*

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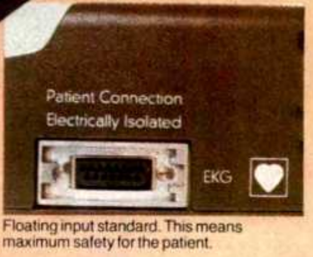

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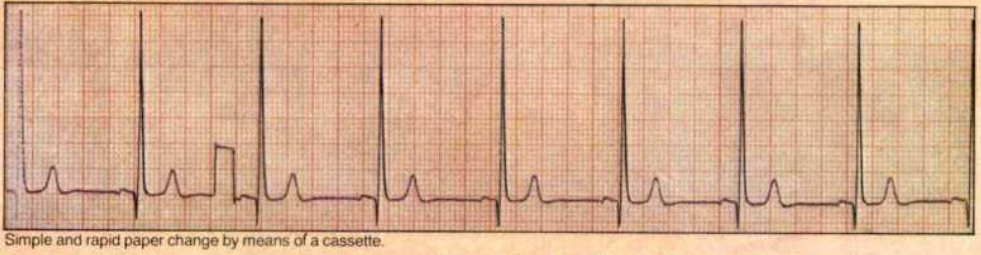

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Free adrenaline and noradrenaline excretion related to occupational stress

MARIO TIMIO, SIMONETTA GENTILI, AND SERGIO PEDE

From Institute of Patologia Speciale Medica e Metodologia Clinica, University of Perugia, Policlinico Monteluce, Perugia, Italy

SUMMARY Urinary levels of free adrenaline and noradrenaline were measured in two groups of healthy male industrial workers exposed to alternate four-day periods of working conditions with and without time stress, to test the hypothesis that the sympathetic nervous system is overactivated by occupational stress. Thirty confectionery workers alternated piece-work (payment by results) and work with a fixed daily wage while 30 metal workers alternated work on an assembly line with work off it. Under time stress urinary free adrenaline was 450 per cent and noradrenaline 230 per cent of the levels for similar work without time stress but involving equal oxygen consumption. These differences were statistically highly significant and they persisted on retesting after six months of alternating work regimens. They support the concept that occupational stress in industrial workers influences the adrenosympathetic system and they indicate a possible method for assessing the effects of high levels of sympathetic activity on the aetiology of ischaemic heart disease.

Urinary free adrenaline and noradrenaline excretion provides a general measure of sympatho-adrenal response to stress (von Euler, 1964). This measurement has been used by Bellet *et al.* (1969), Anitesco (1972), Klimmer (1972), Levi (1972b), and Carruthers *et al.* (1976) to evaluate the role of the sympathetic nervous system in some forms of occupational stress. However, few attempts have been made to assess adrenosympathetic activity in certain common types of work, such as piece-work and on the assembly-line.

The purpose of the present study was to extend our earlier observations (Timio and Gentili, 1976) to a larger group of workers, with particular reference to assessing the role of the sympathetic nervous system by contrasting measurements of urinary free adrenaline and noradrenaline excretion in men under conditions of time stress at work (piece-work and on the assembly-line) with similar work without time stress. In addition this study was designed to ascertain whether the adrenosympathetic reaction becomes altered after a six-month period of intermittent exposure to both work systems.

Subjects and methods

Sixty male industrial workers took part in this research. The age range was 22 to 42 years, mean 34 years. All subjects were in good health and had normal 12 lead electrocardiogram, blood pressure, and glomerular filtration rate (performed a few days before the observation). The aim and procedure of the study were explained to all workers and their signed consent obtained.

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They were divided into two groups according to their job:

Group 1: 30 confectionery workers (piece-workers, paid by results);

Group 2: 30 metal workers (assembly-line workers).

They were all trained. All had worked at the same trade for more than one year, predominantly on piece-work or on the assembly-line. To avoid the possibility that the hormonal response of the workers might have been conditioned in advance because we had told them the aim of the study, a cross-over design was used, dividing each group into two subgroups of 15 workers. Each subgroup was investigated for three periods of four consecutive working days (seven hours daily) according to the following schedules.

Schedule A: the first subgroup of confectionery workers started under piece-work conditions, continued on a fixed daily wage, then performed piece-work again (piece-work/fixed wage/piece-work).

Schedule B: the second subgroup of confectionery workers, after the first period on a fixed wage, continued on piece-work, and then returned to a fixed wage (fixed wage/piece-work/fixed wage).

Schedule C: the first subgroup of metal workers worked on the assembly-line, performed work off the assembly-line during the second period, and then returned to the assembly-line (assembly-line/off-the-line/assembly-line).

Schedule D: the second subgroup of metal workers began with off-the-line work, continued on the assembly-line, then performed off-the-line work again (off-the-line/assembly-line/off-the-line).

Muscular work expressed as average energy cost (MJ/minute[1]) was similar on piece-work (7·35 ± 0·50) and fixed wage days (7·30 ± 0·46), and on assembly-line (8·10 ± 0·76) and off-the-line work days (8·15 ± 0·80). Energy expenditure was calculated in terms of the oxygen consumed in litres of expired air per minute (1 litre of oxygen consumed by a worker is equivalent to 21 MJ). The expired air was collected in a Douglas bag for 10 minutes of every workday of a given task (Zenz, 1975).

To minimise methodological errors we adopted a standard procedure. During the periods of observation food intake was free of any substance that might have influenced urinary catecholamine excretion; all drinks containing ethanol or caffeine were prohibited. No worker was taking psychotrophic substances, oral sympathomimetics, or sympathicolytics, tetracyclines, or inhaled vasoconstrictor substances for nasal stuffiness.

Each subject was instructed not to smoke from the time he awoke to the end of his working day. Working environmental temperature was constant at optimal levels (17° to 20°C).

Each worker started work at 7.00 am after an overnight rest and a standard breakfast. Each emptied his bladder some five to 10 minutes before he started work. Urine collections were made over the seven-hour working period in bottles containing 10 ml 6N HCl and stored at 4°C. The storage period never lasted more than 24 hours.

Determinations of urinary excretion of free adrenaline and noradrenaline were made blind, using the spectrofluorimetric method described by Valori *et al.* (1970). The quantity of each amine was estimated differentially by solving two simultaneous equations in which fluorescence readings were corrected for the blank values. However, in our procedure, reagent blank values were low, reproducible, and very stable. In order to compensate for any incomplete urine collections, the catecholamine results were expressed as μg per g creatinine, as suggested by von Euler (1964). Creatinine was determined by alkaline picrate method.

Student's t test for paired data was used for statistical analysis. All values are given as mean ± standard error of means. Serial determinations of free adrenaline and noradrenaline urinary excretion were repeated in the same subjects after six months, during which time they alternated weeks under time-stress in piece-work or on the assembly-line with weeks of fixed wages or off-the-line work. The standard procedure, cross-over design, and chemical method were identical to those adopted for the first observation.

Results

STANDARD GROUP

The urinary excretion of adrenaline and noradrenaline in 10 male normal control subjects (age range: 24 to 43 years, mean age 33) during 7 hours (from 7.00 am to 2.00 pm) of light work was for adrenaline: 1·24 ± 0·51 μg/g creatinine; and for noradrenaline: 7·19 ± 1·1 μg/g creatinine.

GROUP 1

The seven-hour adrenaline and noradrenaline excretion in the confectionery workers increased steadily throughout the four days of piece-work, during both A and B schedules; the mean levels are presented in Table 1. During fixed wage days the urinary levels of adrenaline and noradrenaline were low and did not differ from those in the control

Table 1 *Mean levels (± SEM) for urinary adrenaline and noradrenaline excretion (μg/g creatinine/7 h) during four-day periods of piece-work and fixed wages in schedules A and B*

Schedule	*Work*	*Adrenaline*		*Noradrenaline*	
		Mean ±	*SEM*	*Mean ±*	*SEM*
A	Piece-work	5·83	0·98	20·02	1·82
	Fixed wage	1·12	0·27	8·12	0·78
	Piece-work	5·36	1·01	18·83	1·96
B	Fixed wage	1·28	0·39	10·04	0·62
	Piece-work	6·03	1·18	22·19	2·31
	Fixed wage	1·11	0·44	9·15	1·01

Table 2 *Mean levels (± SEM) of urinary adrenaline and noradrenaline excretion (μg/g creatinine/7 h) during four-day periods of piece-work and fixed wages in schedules A and B in same workers after six months*

Schedule	*Work*	*Adrenaline*		*Noradrenaline*	
		Mean ±	*SEM*	*Mean ±*	*SEM*
A	Piece-work	4·29	0·83	23·19	2·98
	Fixed wage	1·01	0·21	9·01	1·12
	Piece-work	5·18	1·12	19·13	2·01
B	Fixed wage	1·61	0·39	8·16	0·98
	Piece-work	6·13	2·01	22·58	2·11
	Fixed wage	1·18	0·19	10·01	1·09

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[1] kCal ≈ 4·2 MJ.

men doing light work. The differences between piece-work and fixed wage periods in both subgroups were highly significant ($P < 0{\cdot}001$).

After six months, the measurement of excreted free adrenaline and noradrenaline again showed raised levels in both subgroups of confectionery workers during the four days of piece-work compared with the fixed wage periods (Table 2). The change was statistically significant ($P < 0{\cdot}01$).

GROUP 2

During each period of assembly-line work performed in accordance with schedules C and D, the mean seven-hour levels of urinary adrenaline and noradrenaline in metal workers were significantly higher ($P < 0{\cdot}01$) than those found during off-the-line work (Table 3). The excretion of both catecholamines was similar to the value of control men doing light work at all times of off-the-line work.

Table 3 *Mean levels (± SEM) of urinary adrenaline and noradrenaline excretion (μg/g creatinine/7 h) during four-day periods of assembly-line and off-the-line work in schedule C and D*

Schedule	*Work*	*Adrenaline*		*Noradrenaline*	
		Mean ±	*SEM*	*Mean ±*	*SEM*
C	Assembly-line	5·53	1·08	21·13	2·96
	Off-the-line	1·08	0·22	9·11	1·36
	Assembly-line	6·01	1·12	19·18	2·49
D	Off-the-line	1·17	0·28	8·06	1·14
	Assembly-line	5·13	1·06	21·38	2·07
	Off-the-line	1·04	0·23	10·12	1·35

Measurement of urinary free adrenaline and noradrenaline after six months showed a high level throughout each period of assembly-line work, compared with low values obtained during off-the-line work (Table 4). The difference was significant ($P < 0{\cdot}01$) for both catecholamines.

Table 4 *Mean levels (± SEM) of urinary adrenaline and noradrenaline excretion (μg/g creatinine/7 h) during four-day period of assembly-line and off-the-line work in schedules C and D in same workers after six months*

Schedule	*Work*	*Adrenaline*		*Noradrenaline*	
		Mean ±	*SEM*	*Mean ±*	*SEM*
C	Assembly-line	6·14	1·96	19·46	2·04
	Off-the-line	1·26	0·33	10·13	1·14
	Assembly-line	5·36	1·68	21·16	2·48
D	Off-the-line	1·04	0·19	10·18	1·06
	Assembly-line	4·93	1·51	23·72	3·12
	Off-the-line	1·22	0·25	8·41	0·97

Discussion

The aim of the present study was to describe the effects of two common working systems with respect to the adrenosympathetic response which they produced in men.

The results extend our earlier report (Timio and Gentili, 1976) and represent the first serial measurement of adrenaline and noradrenaline during piece-work and assembly-line work. They support the assumption that such working factors have a significant effect on the sympathetic function in normal subjects. A previous investigation consisted of a few measurements of urinary catecholamines performed by Levi (1972b) in 12 healthy female invoicing clerks, under experimental conditions very similar to piece-work. He found a significant increase in urinary adrenaline and noradrenaline excretion, with a concomitant increase in distress, as judged by increment in rush, fatigue, and physical discomfort ratings.

In 60 healthy male blue-collar workers under piece-work and assembly-line conditions, we have observed an increase in the urinary level of free adrenaline and noradrenaline. The increase remained almost unchanged (450% and 230% of the mean normal values) thoughout the four days of observation. During fixed wage days and off-the-line work, measurements of both catecholamines were low and equalled those of controls doing light work, though the muscular work (as measured by oxygen consumption) of confectionery workers and metal workers was identical to that on days of piece-work and assembly-line work.

The difference in urinary catecholamine excretion between the two time stressed and unstressed working conditions persisted not only throughout each four-day period of observation, but also after six months of alternate exposure to time stress and unstressed working conditions.

The basic physiological mechanisms leading to the high levels of catecholamines in these subjects, to some degree accustomed to their routine, are not straightforward, since habituation to normal environmental stimuli might be expected to lead to a decrease in psychoendocrine reaction intensity (Levi, 1972a). On the other hand, the possible effect on the adrenosympathetic response resulting from awareness of the aim of the investigation was avoided by a cross-over design involving the division of each group of workers into two subgroups with alternate schedules of work. One might hypothesise that the significant adrenosympathetic reaction occurring from a repetition of psychological working stress is the net effect of prolonged exposure (increasing the levels) and of habituation (decreasing the levels).

Analysis of multiple factors that promote adrenergic drive, quantification of their relative importance, and the identification of the source of the increased urinary excretion of catecholamines in normal subjects under conditions of work stress are difficult. Henry *et al.* (1971), studying the effects of environmental behavioural influences on the cardiovascular system, noted an increase in the catecholamine-synthesising enzyme tyrosine-hydroxylase and phenyletanolamine N-methyltransferase in mice exposed for prolonged periods to substained psychosocial stress. Even though the experimental animal metabolic response to environmental stress may have aspects that mimic human conditions, the importance of these results, extrapolated to man, is only conjectural.

Although there is some experimental evidence to link increased adrenergic activity with the development of atherosclerosis and coronary heart disease (Haft and Fani, 1973), further research is needed to assess the suggestion that the adrenosympathetic overactivity observed in men under modern working conditions predisposes towards disease of the coronary arteries.

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Extracardiac defects in children with congenital heart disease

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SUMMARY Extracardiac defects were found in 66 (13%) of 513 Nigerian children with congenital heart disease. As a group these 66 children were significantly younger than the remaining 447 children who had congenital heart disease without extracardiac defects. Of the extracardiac defects, 27 per cent occurred in the musculoskeletal system, 23 per cent in the gastrointestinal tract, and 7·5 per cent in the central nervous system. In addition, 15 (23%) and eight (12%) of the 66 children had congenital rubella and Down's syndrome, respectively. With the exception of the well-recognised association between Down's syndrome and endocardial cushion defect, and between congenital rubella syndrome and persistent ductus arteriosus no extracardiac defects appeared to be predictably associated with any specific form of congenital heart disease. The extracardiac defects caused the death of 12 per cent of the patients in the newborn period; and 17 (52%) of 33 surviving patients have mental retardation.

Extracardiac defects should be carefully looked for in children with congenital heart disease because early detection and treatment of the non-cardiac defects could improve the overall prognosis. Where facilities for cardiac surgery are limited priority for corrective surgery should be given to patients who have no mental handicaps since they are more likely to derive maximum benefits from the expensive surgical procedures.

Since most types of congenital heart disease are now amenable to surgery (Aberdeen, 1975; Morris and McNamara, 1975), it is essential that any child with congenital heart disease should be completely evaluated, noting in particular congenital extracardiac defects which may adversely affect the prognosis. Such an evaluation demands, among other things, a knowledge of the incidence and clinical significance of extracardiac defects in children with congenital heart disease. However, previous reports on the subject (Abbott, 1927; Okada *et al.*, 1968; Blankson and Christian, 1975) have given divergent estimates of the incidence of extracardiac defects in such children, and very little attempt has been made to assess the significance of such non-cardiac defects. The present study was therefore undertaken with a view to determine the incidence, distribution pattern, and clinical significance of extracardial defects in Nigerian children with congenital heart disease.

Subjects and methods

Between 1965 and 1978, 513 children with congenital heart disease were studied at the University College Hospital, Ibadan. Of these children, 66 had associated extracardiac defects and they formed the subjects of the present study. In 47 of these 66 patients the diagnosis of congenital heart disease was based on clinical and angiocardiographic findings while the extracardiac defects were diagnosed on the basis of characteristic clinical and radiological features. The clinical diagnoses were confirmed by chromosome studies in appropriate cases. The mental development of the patients was assessed by comparing their levels of psychomotor development, social intercourse, speech acquisition, and learning aptitude with those of healthy subjects attending the children's welfare clinic in our hospital. A patient was judged to be mentally retarded if he was subnormal by three or four of the indices that we employed. However no developmental assessment was attempted in patients aged less than one year because we have found that such assessments are often inaccurate in young infants. In the remaining 19 patients both congenital heart disease and extracardiac defects were confirmed at necropsy (Antia, 1974).

For the purposes of this study congenital rubella syndrome and Down's syndrome were classified as single defects.

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Table 1 *Age distribution of patients with congenital heart disease and associated non-cardiac defects*

Age	*No. of patients*	*Per cent*
Birth to 1 month	12	18
1 month to 1 year	21	32
1 to 5 years	14	21
Above 5 years	19	29
Total	66	100

Results

INCIDENCE OF EXTRACARDIAC DEFECTS

The age groups of the 66 patients with extracardiac defects are shown in Table 1: 50 per cent of them were aged 1 year and less. As a group they were also significantly younger (mean age ±SEM = 15 ± 0·29 months) than the other 447 patients (mean age ±SEM = 35 ± 0·28 months) who had congenital heart disease without associated extracardiac defects ($t=3{\cdot}9$; $P<0{\cdot}01$). There was no significant difference in the sex distribution of the 66 patients, their male to female ratio being 1 to 1·3. The overall incidence of extracardiac defects in all 513 patients with congenital heart disease was 13 per cent (Table 2). However the incidence was lower (10%) in the clinical compared with the necropsy series (35%). Multiple extracardiac defects were encountered in 13 patients, but the average number of defects per patient was 1·2.

ASSOCIATION PATTERNS OF EXTRACARDIAC DEFECTS

If all the extracardiac defects are considered as a group 17 per cent of them occurred in association with complex cardiac lesions like transposition of the great arteries, tricuspid atresia, and endocardial cushion defect; 15 per cent and 13 per cent occurred in association with ventricular septal defect and persistent ductus arteriosus, respectively (Table 2). Isolated pulmonary stenosis and Fallot's tetralogy were associated with the least number of extracardiac defects. These differences were, however, not statistically significant ($P>0{\cdot}05$).

Three of the eight patients with Down's syndrome had endocardial cushion defects as evidenced by a combination of ventricular septal defects and congenital mitral regurgitation (Table 3). The remaining five patients had auscultatory signs of uncomplicated ventricular septal defects. However their mean electrical QRS axes ranged between 270° and 330°; it is, therefore, reasonable to conclude that they too had endocardial cushion defects (Rudolph, 1974). Thus the incidence of Down's syndrome in patients with endocardial cushion defects (80%) was significantly higher than the 12 per cent incidence of Down's syndrome in the entire study ($\chi^2=20{\cdot}2$; $P<0{\cdot}001$). Similarly, 10 (77%) of the 13 patients with persistent ductus arterious had associated congenital rubella syndrome; this incidence was significantly higher than the 23 per cent incidence of congenital rubella syndrome in the entire study ($\chi^2=14{\cdot}8$; $P<0{\cdot}001$). All four patients with ostium secundum type of atrial septal defect had musculoskeletal defects, but the number of patients was too small for statistical evaluation. Though over 50 per cent of the gastrointestinal defects occurred in patients with ventricular septal defect the association did not achieve statistical significance ($P>0{\cdot}05$).

TYPES OF EXTRACARDIAC DEFECT

Musculoskeletal defects were the commonest and accounted for 27 per cent of all extracardiac defects (Table 4). The spectrum ranged from single defects like syndactyly and cleft palate (two cases of each) to multiple defects as in Edwards', Ellis-van Creveld, Holt-Oram, Noonan's, and Turner's syndromes (one case of each). Of the patients, 23 per cent had defects in the gastrointestinal tract. These included umbilical and inguinal hernias (seven cases), tracheo-oesophageal fistula (four

Table 2 *Prevalence of extracardiac defects in children with congenital heart disease*

	Clinical series		*Necropsy series*		*Both series combined*	
Type of coronary heart disease	*No. of patients*	*Centile with extracardiac defects*	*No. of patients*	*Centile with extracardiac defects*	*No. of patients*	*Centile with extracardiac defects*
Ventricular septal defect	135	11	9	67	144	15
Persistent ductus arteriosus	96	12	6	33	102	13
Atrial septal defect	40	10	4	0	44	9
Pulmonary stenosis	47	8·5	3	0	50	9
Fallot's tetralogy	48	2	12	33	60	9
Miscellaneous complex lesions (triscuspid atresia; transposition of great arteries; endocardiac cushion defect, etc)	92	13	21	33	113	17
All defects	458	10	55	35	513	13

Table 3 *Prevalence of extracardiac defects in each form of congenital heart disease*

	Congenital heart disease					
	Ventricular septal defect	*Persistent ductus arteriosus*	*Atrial septal defect*	*Endocardiac cushion defect*	*Others*	*Total*
Extracardiac defects						
Gastrointestinal defect	8	1	—	—	6	15
Down's syndrome	—	—	—	8	—	8
Congenital rubella syndrome	5	10	—	—	—	15
Musculoskeletal defects	5	—	4	2	7	18
Others	3	2	—	—	5	10
Total	21	13	4	10	18	66

cases), duodenal atresia (two cases), and one case each of imperforate anus and omphalocele. Fifteen patients had congenital rubella syndrome, eight had Down's syndrome, and three others had spina bifida. There were two cases of renal cysts and one case each of bifid uterus and posterior urethral valve.

CLINICAL SIGNIFICANCE OF EXTRACARDIAC DEFECTS

Non-cardiac defects appeared to have been the immediate or major cause of death in eight (12%) of the 66 patients; and all the deaths occurred in the newborn period. Seven of these eight patients had gastrointestinal defects (Table 5). Of the three patients with tracheo-oesophageal fistula, two died during surgical correction of the defect. The third patient presented in hospital on the second day of life with cyanosis and clinical and radiographic features of tracheo-oesophageal fistula and aspiration pneumonia. This patient died a few hours after admission; necropsy confirmed the clinical diagnosis and also disclosed a coexisting transposition of the great arteries. Two patients with duodenal atresia and another with imperforate anus and gall-bladder atresia died of severe fluid and electrolyte disturbance, while the baby with omphalocele succumbed to a coliform septicaemia. The eighth patient, a 5-day-old baby, had persistence of the fetal circulatory pattern with pulmonary hypertension, right-to-left ductal shunt, and fatal hypoxaemia. Necropsy subsequently disclosed a hypoplastic right lung with the ipsilateral pulmonary veins draining into the inferior vena cava.

The mental development of 33 of the surviving patients was assessed: 17 of them (52%) were mentally retarded, including eight patients with Down's syndrome, seven with congenital rubella syndrome, and two other patients whose neurological features did not fit into any recognised syndrome.

Discussion

The reported incidence of extracardiac defects in children with congenital heart disease varies from 11 to 44 per cent and, with one exception (Emerit *et al.*, 1967), the lowest incidence rates have been recorded in clinical (Lamy *et al.*, 1957) and the highest in necropsy studies (Wallgren *et al.*, 1978). The highest incidence in necropsy studies, which is also confirmed by our data, may be partly because necropsies are likely to disclose minor organ defects (for example bifid uterus, single renal cyst) which could easily be missed in clinical studies. Furthermore some extracardiac defects may cause death in the newborn period or early infancy. Such defects would therefore be more prevalent in necropsy studies which invariably include a large number of infants (Wallgren *et al.*, 1978). But despite the

Table 4 *Pattern of extracardiac defects*

Type of defects	*No. of patients*	*Centile*
Musculoskeletal*	18	27
Gastrointestinal	15	23
Rubella syndrome	15	23
Down's syndrome	8	12
Neurological*	5	7·5
Urogenital	4	6
Pulmonary hypoplasia	1	1·5
Total	66	100

*Excluding patients with Down's and congenital rubella syndromes.

Table 5 *Fatal extracardiac defects in 8 patients*

Extracardiac defect	*Cardiac lesion*
Tracheo-oesophageal fistula	Ventricular septal defect
Tracheo-oesophageal fistula	Fallot's tetralogy
Tracheo-oesophageal fistula	Transposition of great arteries
Duodenal atresia	Ventricular septal defect
Duodenal atresia	Persistent ductus arteriosus
Omphalocele	Transposition of great arteries
Imperforate anus, gall-bladder atresia	Ventricular septal defect
Hypoplastic right lung	Persistent ductus arteriosus, partial anomalous pulmonary venous drainage

Table 6 *Comparison of incidence of some congenital extracardiac defects in general population (Gupta, 1969) and in children with congenital heart disease*

	Incidence (%)	
Defects	*General population*	*Present study*
Gastrointestinal		
Inguinal hernia	0·16	1·0
Imperforate anus	0·03	0·2
Omphalocele	0·03	0·2
Duodenal or ileal atresia	0·02	0·4
Gall-bladder atresia	0·02	0·2
Tracheo-oesophageal fistula	0	0·8
Musculoskeletal		
Defects of long bones	0·10	2·8
Cleft lip and palate	0·08	0·4
Syndactyly	0·04	0·4
Central nervous system		
Spina bifida	0·07	0·6
Other defects	2·45	6·0
Overall incidence	3·0%	13·0%

($\chi^2=107$, $P<0{\cdot}001$)

probability that clinical studies underestimate the prevalence of extracardiac defects in children with congenital heart disease the incidence rates so determined are still considerably higher than the general incidence of birth defects which has been estimated at between 1 and 7 per cent (McIntosh *et al.,* 1954; Harris, 1974). Table 6, which includes data obtained by Gupta (1969) in a study of 4,220 consecutive deliveries at a general hospital in Ibadan, clearly shows the excess of extracardiac defects in children with congenital heart disease. Indeed Kenna *et al.* (1975) have estimated the incidence of associated defects in children with congenital heart disease at about 10 times the chance expectation. This excess of extracardiac defects may be explained on the basis of a clustering of defects produced by the action of a pluripotent teratogen on a susceptible fetus.

About half the extracardiac defects in our patients occurred in the musculoskeletal and gastrointestinal systems. This preponderance of skeletal and gastrointestinal defects, which has also been noted by other workers (Macmahon *et al.,* 1953; Wood *et al.,* 1969), is probably because the structural development of the cardiovascular, gastrointestinal, and musculoskeletal systems occurs concurrently between the third and eighth weeks of fetal life (Arey, 1974). Therefore any teratogen acting on one of these three systems at that vulnerable period could affect the other two. Our data suggests, however, that in a majority of cases the teratogens have no predilection for any specific tissues. Thus, with the exception of the well-recognised association between congenital rubella and persistent ductus arteriosus (Campbell, 1961) and between Down's syndrome and septal defects (Berg *et al.,* 1960; Park *et al.,* 1977) no extracardiac defect appears to be predictably associated with any specific congenital heart disease. Similar findings have also been reported by Menashe *et al.* (1967), and Wallgren *et al.* (1978).

In the technically developed countries with abundant health facilities mental retardation is not a contraindication to cardiac surgery, and open-heart operations are performed even on patients with Down's syndrome (Esplugas *et al.,* 1976). With the background of limited financial and health resources in many developing countries, however, a cost/benefit analysis would show that even where the facilities exist priority for cardivascular surgery should be given to patients who have no major mental or other handicaps and can thus derive maximum benefits from such expensive procedures.

Death may result from metabolic derangements caused by extracardiac defects, or during surgical treatment of such defects. Less frequently extracardiac defects may aggravate haemodynamic derangements initiated by congenital heart disease. For instance pulmonary hypoplasia, which may be isolated as in one of our patients, or associated with a diaphragmatic hernia (Dibbins and Wiener, 1974; Dibbins, 1976) may exacerbate the normal pulmonary hypertension of the newborn, perpetuate the fetal circulatory pattern, and precipitate cardiac failure. In the present series death was attributable to extracardiac defect in 12 per cent of the patients, and higher figures have indeed been reported from other centres (Kenna *et al.,* 1975; Wallgren *et al.,* 1978). This mortality is considerable, and it emphasises the need for a thorough evaluation of any child with congenital heart disease since early detection and treatment of these non-cardiac defects could improve the prognosis.

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Case reports

British Heart Journal, 1979, **42**, 480–482

Renal artery stenosis with severe hypertension
A rare case with detailed assessment of renin-angiotensin system before and after development of lesion

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SUMMARY The rare opportunity arose to assess in detail the renin-angiotensin system before and after the development of a renal artery stenosis with severe hypertension. Peripheral plasma concentrations of renin, angiotensin II, and aldosterone were known to be normal before the development of renal artery stenosis, and there were no lateralising features on renal vein sampling. Acute hypertension associated with very high peripheral plasma concentrations of renin and angiotensin II, and with pronounced lateralisation on renal vein sampling followed the development of acute unilateral renal artery stenosis. These measurements all returned to normal after nephrectomy, conforming with the pattern of changes previously established only in experimental animals.

Unilateral renal artery constriction is a classical means of inducing experimental hypertension (Goldblatt *et al.*, 1934), and renal artery stenosis is a well recognised, potentially correctable cause of clinical hypertension (Foster *et al.*, 1975). After constricting a renal artery in animals, blood pressure rises within hours and this can be accounted for quantitatively by the direct pressor action of the concomitant increase in plasma angiotensin II (Caravaggi *et al.*, 1976). Later in the course of hypertension, peripheral plasma concentrations of angiotensin II are lower in relation to arterial pressure (Brown *et al.*, 1979) and it is in this second phase that renovascular hypertension is usually first encountered in man. It is rare clinically to observe the evolution of renal artery stenosis with hypertension, and detailed biochemical assessment before and after the development of such a lesion has not, to our knowledge, been reported previously. The following account describes the development of unilateral renal artery stenosis and severe hypertension in a patient in whom detailed investigations one year earlier had disclosed no relevant abnormality.

Case report

The patient, a 33-year-old labourer, first presented in February 1976 with a subarachnoid haemorrhage caused by a ruptured berry aneurysm of the posterior communicating artery. At craniotomy clipping of the aneurysm was technically impossible. After the operation his blood pressure was 150/106 mmHg. Propranolol (80 mg daily) was introduced as an out-patient and blood pressure control was good, averaging 120/78 mmHg on four visits to his general practitioner.

In February 1977 the patient was referred to the MRC Blood Pressure Unit for assessment and after one month without treatment he was admitted for investigation. Arterial pressure was then 140/102 mmHg (mean of six readings) and his optic fundi were normal. Physical examination did not demonstrate any cause for the increase in blood pressure. He smoked 20 cigarettes a day. There was no family history of hypertension, though his father had died, aged 51, after a myocardial infarction. Investigation (March 1977) in the metabolic ward on a fixed known and normal intake of sodium and potassium, revealed in samples taken at 08.30 a.m., after overnight recumbency and fasting, normal serum electrolytes (sodium 142 mmol/l, potassium 4·3 mmol/l, bicarbonate 24 mmol/l) and peripheral plasma concentration of active renin—18 μU/ml (normal range 9–50 μU/ml; Millar *et al.*, 1978), angiotensin II—19 pmol/l (normal range 5–35 pg/ml; Dusterdieck and McElwee, 1971), and aldosterone—11 ng/100 ml (305 pm ol/l) (normal range < 18 ng/100 ml (< 499 pmol/l); Fraser *et al.*, 1973). Other normal results were blood urea (4·2 mmol/l) and creatinine (86 μmol/l), creatinine clearance (85 ml/min), fasting lipids, urinary normetadrenaline, electrocardiogram, and chest *x*-ray. Exchangeable sodium and potassium were 91·7 per cent and 99·2 per cent of the expected values, respectively (Davies and Robertson, 1973). An intravenous pyelogram was normal, apart from a suspicion of a small calyceal cyst on the right side. Because of this finding and the patient's age, plasma concentrations of renin and angiotension II were estimated in blood samples taken from the renal veins (Semple *et al.*, 1979) and these were normal with no suggestion of a unilateral lesion (Table 1).

After discharge from hospital, blood pressure was well controlled by propranolol (80 mg daily): April 1977, 136/84 mmHg; August 1977, 134/86 mmHg; October 1977, 140/88 mmHg; and February 1978, 136/86 mmHg. However, at his next outpatient visit in May 1978, after severe frontal headaches for three weeks, he was readmitted with a blood pressure of 210/144 mmHg and bilateral retinal haemorrhages and exudates, though no papilloedema were present. Blood pressure was reduced, but not to normal (176/108 mmHg, mean of 10 readings) with atenolol (200 mg daily), minoxidil (20 mg daily), and frusemide (80 mg daily).

His intravenous pyelogram now showed typical features of right-sided renal artery stenosis (Brown *et al.*, 1960) with delayed excretion of contrast on the right side and with increased concentration of dye both before and after a water load. Arteriography confirmed that he had developed a tight 1 cm long stenosis beginning 4 mm from the origin of his right renal artery. Repeat renal vein sampling (Table 1) then showed a distinct excess of renin in plasma from the right renal vein contrasted with the negative venoarterial difference across the left kidney, indicating net extraction of renin by the unaffected contralateral kidney. Angiotensin II levels in renal vein plasma were also consistently higher on the right than on the left. These were, therefore, classical findings of unilateral renal artery stenosis (Millar *et al.*, 1978; Semple *et al.*, 1979). Divided renal function studies (Table 2) also showed changes characteristic of right renal artery stenosis (Brown *et al.*, 1960).

In an effort to correct the hypertension, a right aortorenal bypass graft was inserted in June 1978 but the graft thrombosed within five days and his blood pressure remained high. The infarcted right kidney was removed one week later. The blood pressure fell by 10 days after nephrectomy to 164/104 mmHg and was controlled easily with atenolol 100 mg daily. Three months after operation beta-adrenergic blockade was withdrawn and blood pressure thereafter remained consistently less than 140 mmHg systolic, 90 mmHg diastolic. Six months after the operation, repeat estimations of peripheral plasma concentrations of active renin, 24 μU/ml,

Table 1 *Renal vein sampling*

	Active renin (μU/ml)						*Angiotensin II (pmol/l)*					
	March 1977			*May 1978*			*March 1977*			*May 1978*		
	Samples			*Samples*			*Samples*			*Samples*		
	1	*2*	*3*	*1*	*2*	*3*	*1*	*2*	*3*	*1*	*2*	*3*
Left renal vein	14	16	16	344	308	372	13	13	14	39	40	48
Right renal vein	15	15	17	535	902	999	15	13	18	52	80	68
Aorta	15	14	16	360	347	467	14	17	15	71	89	90

Active renin levels (normal range 9 to 50 μU/ml) and angiotension II levels (normal range 5 to 35 pmol/l) on simultaneous sampling from the left renal vein, right renal vein, and aorta. In March 1977 the patient was on no drugs, in May 1978 he was on frusemide, prazosin, and hydralazine.

Table 2 *Divided renal function study*

Plasma Creatine μmol/l	*PAH μmol/l*	*Period No.*	*Min*	*Urine ml/min*		*Na⁺*	*mmol/l*	*Creat. mmol/l*		*PAH mmol/l*		C_{Cr} *ml/min*		C_{PAH} *ml/min*	
				L	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*
112	97	1	4	8·1	2·4	60	27	0·88	1·67	4·30	9·18	64	36	359	227
104	105	2	4	9·5	2·6	50	18	0·89	1·71	4·44	9·64	81	43	402	239
107	115	3	4	8·0	2·6	50	34	0·81	1·22	4·00	6·76	61	30	278	153
104	118	4	4	8·5	2·6	45	17	0·81	1·45	4·20	8·10	66	36	303	178

Note: The lower urine volume and sodium concentration on the right and the higher creatinine and PAH concentration are typical of right renal artery stenosis (Brown *et al.*, 1960).

angiotensin II, 20 pmol/l, and aldosterone, 8 ng/100 ml (222 pmol/l) were all normal in samples obtained in recumbency.

Discussion

As far as we are aware, detailed assessment of the renin-angiotensin-aldosterone system, and in particular renal vein renin and angiotensin II values, have not been described previously in man before and after a renal artery stenosis of rapid onset. However, Adams and Newman (1958), Laidlaw *et al.* (1960), and Barraclough (1966) describe patients in whom hypertension secondary to renal artery stenosis was noted from 42 days to four months after blood pressure was known to be normal. All of those cases presented with loin pain, suggesting renal infarction, but no such symptoms were present in this case. Our patient previously had a subarachnoid haemorrhage, but since the increased blood pressure associated with that syndrome (Neil-Dwyer and Cruickshank, 1974) is usually short-lived and investigation disclosed no other cause, continuing mild hypertension after craniotomy was not thought to be related to this.

The cause of this patient's renal artery stenosis has not been determined. Arteriographic findings were not typical of fibromuscular hyperplasia and no changes were shown in any other vessels, though the stenosed area was not available for histological examination. Family and smoking histories make atheroma, with or without thrombus formation, the likely cause, though the aorta was not noted to be atheromatous at arteriography.

There is good evidence that the early rise of blood pressure occurring in animals after clipping a renal artery is a result of the associated increase in plasma concentrations of renin and angiotensin II (Caravaggi *et al.*, 1976; Brown *et al.*, 1979). In man, observations before a stenosis develops can only be fortuitous, as in the case described above, where the results of renal vein sampling (Table 1) are consistent with the animal model. Normal blood pressure accompanied normal peripheral plasma renin and angiotensin II after nephrectomy. Rapid loss of blood pressure control (in less than three months) with potentially disastrous cerebral consequences was thus corrected in this young patient by removal of the source of excess renin secretion.

We thank Drs J. J. Brown, A. F. Lever and J. I. S. Robertson for their advice in the preparation of this paper.

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British Heart Journal, 1979, **42**, 483-486

Transposition of the great arteries associated with a double left ventricular outflow tract[1]

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SUMMARY A case is described in which, at semilunar valve level, the aorta and pulmonary artery arose from inappropriate ventricles. Despite this, the outflow tracts to both vessels originated from the left ventricle. Embryologically, it is speculated that this anomaly is the result of normal rotation of the proximal conus, without concomitant truncal inversion, and excessive leftward shift of the proximal conus and conal septum or anterior and rightward deviation of the anterior segment of the ventricular septum. Surgical repair using a double conduit between the right ventricle and pulmonary artery and eft ventricle and aorta, respectively, was unsuccessful.

Definition of specific outflow tract anomalies is often controversial. For example, transposition of the great arteries has variously been defined as a reversal of the anteroposterior relation of the semilunar valves (Goor and Edwards, 1973), any alteration in the position of the great arteries (Abbot, 1927), and the presence of mitral-aortic valve discontinuity as a result of a subaortic conus (Van Praagh *et al.*, 1967). Recently, several authors have favoured a more literal definition, redefining transposition of the great arteries to mean that both great arteries are 'placed across' the septum (trans-ponere means 'placed across') reversing the connection of the great arteries to the *morphological ventricle* (Van Praagh, 1973; Shinebourne *et al.*, 1976). Thus both great arteries arise from morphologically inappropriate ventricles. By the same token, double outlet ventricle is defined as a specific ventriculo-arterial connection in which more than one and a half great arteries arise from the same ventricular or outlet chamber (Kirklin *et al.*, 1973). We have accepted this literal definition of outflow tract anomalies.

However, according to the interpretation of embryological events by Goor and Lillehei (1975), the semilunar valves and outflow tracts of each of the major vessels are derived from different embryological segments. It is reasonable to anticipate, therefore, that the ventricle of origin of a major vessel (at semilunar valve level) may be at variance with that of its outflow tract. In this communication a case will be described in which the left ventricle has a double outflow tract (aortic and pulmonary), but the origin of the great arteries at semilunar valve level is clearly from inappropriate morphological ventricles.

Terminology

We have adopted the terminology recently proposed by Anderson *et al.* (1977) with regard to outflow tract anomalies. The term 'conus' (and its derivatives) is confined to embryological events. In the postnatal, or fully developed heart, the term 'infundibulum' is substituted for 'conus'. Thus the structure interposed between the two semilunar valves is described as the infundibular septum (parietal band of Van Praagh) (Van Praagh *et al.*, 1975). The muscle separating semilunar from atrioventricular valves is termed the ventriculo-infundibular fold regardless of whether it exists in the right or left ventricle. The trabecula septomarginalis (septal band of Van Praagh) (Van Praagh *et al.*, 1975) is an extensive right ventricular trabeculation with, superiorly, anterior and posterior limbs, reinforcing the anterior and inferior borders of many septal defects.

Case report

A 5½-year-old boy had been cyanosed since birth. Chest *x*-ray film showed cardiomegaly and pulmonary plethora while the electrocardiogram

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[1] Supported by a grant from the Stella and Paul Loewenstein Trust Cardiac Fund, University of the Witwatersrand.

showed a mean frontal QRS axis of +60°, with evidence of right atrial and right ventricular englargement. Small R waves were noted in the right chest lead. Cardiac catheterisation at age 6 days established the diagnosis of transposition of the great arteries, mild pulmonary stenosis, and a small ventricular septal defect. A Rashkind septostomy was performed with considerable improvement in oxygen saturation.

During the next 3 years increasing polycythaemia developed requiring multiple venesections. Cerebral thrombosis and hemiplegia occurred at age 1½ years with fairly good recovery. A Blalock-Taussig shunt was performed when the child was 4 years old, with subsequent improvement in oxygen saturation and fall in haematocrit. Recatheterisation at 5½ years confirmed the previous diagnoses. A systolic gradient of 41 mmHg was measured across the pulmonary outflow tract and the systemic oxygen saturation was 75 per cent. When the left ventricular systolic pressure was 70 mmHg, that in the right ventricle was 80 mmHg. Elective surgery was advised.

Using standard cardiopulmonary bypass techniques, a right ventriculotomy was performed and a 2 to 3 mm ventricular septal defect closed with a single horizontal mattress suture. A valved external conduit (16 mm) was then inserted between the right ventricle and right pulmonary artery. A similar conduit (18 mm) was placed between the apex of the left ventricle and left lateral wall of the ascending aorta. Initially, after discontinuing bypass, the haemodynamics appeared satisfactory. However, just before closing the chest, ventricular fibrillation occurred and resuscitation was not successful.

Necropsy confirmed ventricular non-inversion: the morphological right ventricle was right-sided and the morphological left ventricle was left-sided. The aortic valve was anterior, superior, and to the right, above the right ventricle. The pulmonary valve was to the left of, and slightly posterior to, the aortic valve. Though the pulmonary valve was overriding both ventricles (similar to the aorta in the normal heart), there was no direct communication between the right ventricle and the pulmonary valve or artery. Examination of the interior of the left ventricle disclosed two outflow tracts, separated by a muscular ridge (infundibular septum) approximately in a coronal plane (Fig. 1). The aortic outflow tract was dextro-posterior to the pulmonary outflow tract. The interior of the right ventricle (Fig. 2 and 3a) showed a ventricular septal defect 3 mm in diameter (the surgical suture was removed), triangular in shape, and immediately subaortic. It was bounded by the posterior limb of the trabecula septomarginalis, aortic valve, and, on the left, the anterior ventricular septum. The posteroinferior rim of the defect was separated from the tricuspid valve by a 3 to 4 mm band of muscle. A well-developed ventriculo-infundibular fold separated the semilunar and mitral valves though it was only 2 to 3 mm wide below the aortic valve. The pulmonary outflow tract was mildly stenotic at its origin.

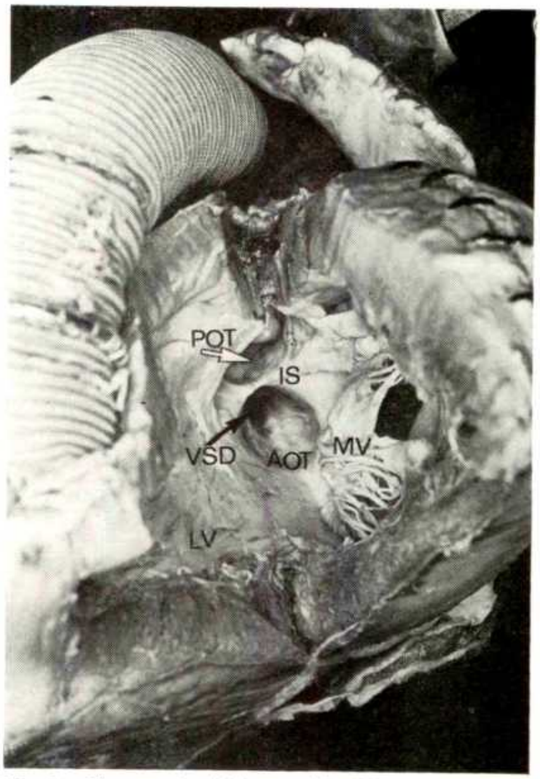


Fig. 1 *Photograph of left ventricle (LV) with double (aortic and pulmonary) outflow tract. The left ventricle has been opened parallel to the left anterior descending coronary artery and immediately to the left of the left ventricular ascending aorta conduit. AOT, aortic outflow tract; IS, infundibular septum; MV, mitral valve; POT, pulmonary outflow tract; VSD, ventricular septal defect.*

Discussion

According to the observations of Goor and Lillehei (1975) and their interpretation of previous embryological descriptions, conotruncal inversion occurs in two stages. Firstly, the conoventricular junction (ostium bulbi) rotates 110° counterclockwise (looking downstream) during d-looping of the cardiac tube. This process transfers the proximal aortic

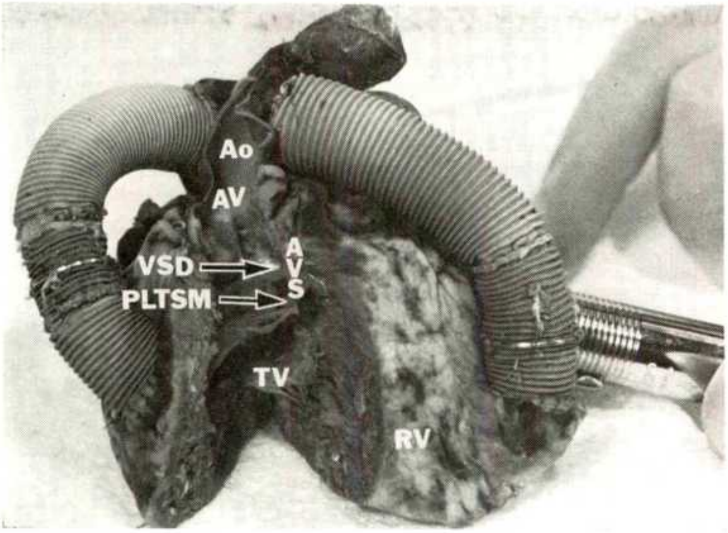
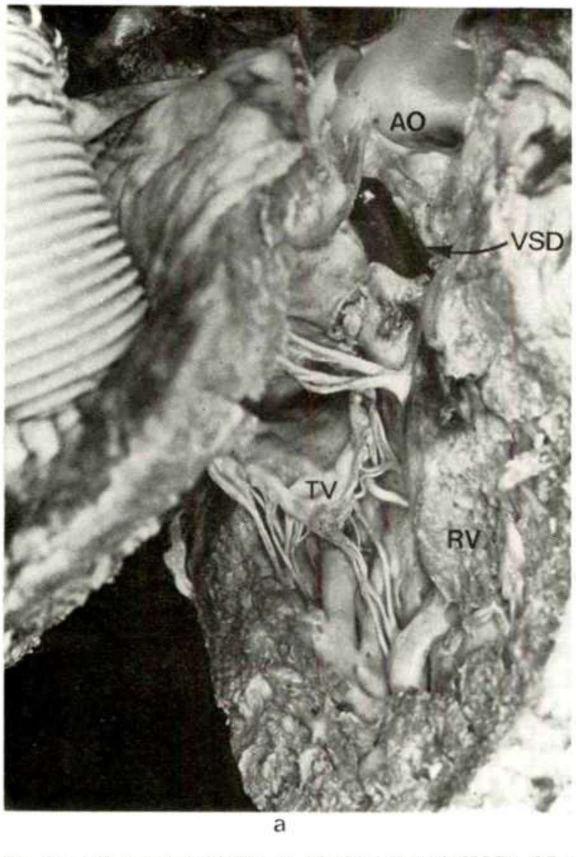


Fig. 2 *Photograph of right ventricle (RV). The anterior wall of the right ventricle has been removed. The ventricular septal defect (VSD) is bounded by the posterior limb of the trabecula septomarginalis (PLTSM), aortic valve (AV), and anterior ventricular septum (AVS).*



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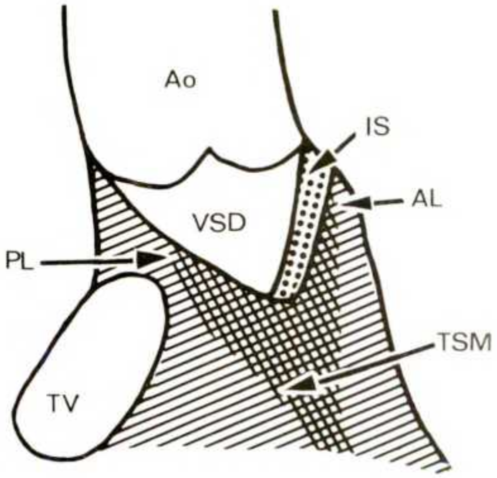

b

Fig. 3a *Closer view of Fig. 2. Marker through VSD. AO, aorta; TV, tricuspid valve.*

Fig. 3b *Diagrammatic representation of relation between infundibular septum (IS) and trabecula septomarginalis (TSM). Ao, aorta; PL, posterior limb; AL, anterior limb; TV, tricuspid valve.*

conus to a posterior (but still right-sided) position and enables it to establish contiguity with the left ventricular vestibulum. At this stage, the conotruncal ridges (destined to form the conal and truncal septa) occupy a spiral course. Secondly, but somewhat later, the truncus (including the developing semilunar valves) rotates in an identical manner. As a result, the conotruncal ridges are uncoiled, the aortic valve is transferred to the same posterior position as the aortic conus, and the aorta and pulmonary artery become entwined—the situation seen in the normal heart. Failure of truncal inversion results in dextroposition of the aortic valve (anterior and rightward displacement) and its origin predominantly, or entirely, from the right ventricle.

In the normal heart, the infundibular septum fills the Y-shaped space between the anterior and posterior limbs of the trabecula septomarginalis. Should this not occur, malalignment of the infundibular and ventricular septa occurs, with a resultant ventricular septal defect and a variety of outflow tract anomalies.

How does transposition occur with a double left ventricular outflow tract? Applying the embryological interpretation of Goor and Lillehei (1975), rotation of the ostium bulbi occurred in our case to account for the posterior position of the aortic outflow tract and coronal plane of the infundibular septum. However, failure of truncal inversion left the aortic valve in its early embryological position, anterior and to the right, above the right ventricle. The muscular ridge in the left ventricle between aortic and pulmonary outflow tracts, which we believe to be the infundibular septum, did not insert between the two limbs of the Y-shaped trabecula septomarginalis. Rather, the infundibular septum, malaligned relative to the ventricular septum, passed through to the left side occupying a coronal plane perpendicular to the plane of the ventricular septum. Subsequent fusion of the infundibular and ventricular septa (and anterior limb of the trabecula septomarginalis) completed the left side of the triangular-shaped ventricular septal defect (Fig. 3b).

The left-sided position of the infundibular septum and hence origin of both outflow tracts and pulmonary valve from the left ventricle may be accounted for by leftward shift of the embryological conventricular junction (Goor and Edwards, 1973; Goor and Lillehei, 1975) or anterior and rightward deviation of the anterior segment of the ventricular septum (Anderson *et al.*, 1974). Though both processes were probably operative, we favour predominance of the latter, because of the relatively normal position of the pulmonary outflow tract and valve relative to the atrioventricular valves.

Incomplete absorption of the subaortic ventriculo-infundibular fold occurred in our case with consequent mitral-aortic fibrous discontinuity. Concomitantly, failure of truncal inversion resulted in the aortic valve and aorta remaining dextroposed and originating completely from the right ventricle.

Although 'posterior' transposition has been previously documented (Van Praagh *et al.*, 1971; Wilkinson *et al.*, 1975), our case is distinctive in that, at semilunar valve level, the aorta was anterior to the pulmonary artery.

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Superior vena cava stenosis at site of intersection of two pacing electrodes

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SUMMARY Superior vena cava obstruction is described in a patient with two endocardial pacing electrodes. At necropsy a severe stenosis of the venous lumen was found at the site of intersection of the two catheters. There was no evidence of thrombus formation. Venous wall stenosis is an unusual complication of transvenous pacing and is probably favoured by the presence of two electrodes.

Adhesion of endocardial pacing electrodes to the venous wall, endocardium, and tricuspid valve has been frequently described (Lagergren *et al.*, 1966; Furman and Escher, 1968; Robboy *et al.*, 1969; Camerini *et al.*, 1973; Contini *et al.*, 1973). Such lesions are usually devoid of clinical significance. However, under special circumstances, severe stenosis may develop, as in the case we describe in this paper.

The patient had two endocardial pacing electrodes (the second had been inserted because of frequent displacement of the first). Several years later he developed superior vena cava obstruction. At necropsy a severe venous stenosis was found at the site of intersection of the two electrodes.

We are unaware of any similar reported case.

Case report

A 55-year-old man was admitted with a one-year history of blackouts. The electrocardiogram showed atrial fibrillation with complete AV block and slow idioventricular rhythm. A permanent pacemaker system was inserted with an Elema EMT 588 endocardial electrode via the right external jugular vein. During the positioning manoeuvres the catheter repeatedly passed into the left atrium and lung fields, and later right heart catheterisation and cineangiocardiography showed that he had an atrial septal defect with left-to-right shunt and severe pulmonary arterial hypertension. During the following months the patient was readmitted to hospital several times with pacing failure. After numerous catheter replacements, a new Sorin C endocardial electrode was inserted via the left external jugular vein without removing the other electrode.

The subsequent period was uneventful until 7 years later, when the patient was readmitted with swelling of the head, neck, and upper extremities, which had developed over a few months. The chest *x*-ray film showed enlargement of the upper mediastinum, thought to be vascular. An isotopic venogram showed complete superior vena cava obstruction with a well-developed collateral circulation, especially via the intercostal veins. The obstruction was thought to be thrombotic in origin and intravenous heparin was started. This being unsuccessful, Urokinase was substituted for heparin. On the fourth day in hospital repetitive bursts of ventricular tachycardia occurred which were resistant to antiarrhythmic drugs. At the end of one of such episodes there was no response to the pacing stimuli and all attempts at resuscitation were unsuccessful.

Necropsy confirmed the clinical diagnosis of atrial septal defect, which was shown to be of the ostium secundum type (Fig. 1), with cardiomegaly (790 g), right ventricular hypertophy, and pronounced pulmonary vascular sclerosis. The Elema catheter (the smaller one) was attached to the septal cusp of the tricuspid valve, with its cut end in the right external jugular vein and the other end lying loose in the right ventricle. The lack of adhesion to the endocardium accounted for the frequent displacements. The Sorin catheter (which was connected to the pacemaker in the left pectoral area) passed via the left innominate vein and was firmly wedged in the trabecular system with extensive fibrous reaction. At the site where the two electrodes interesected (Fig. 2), at the junction of the innominate veins and the superior vena cava, there was severe stenosis of the lumen. The stenotic area,

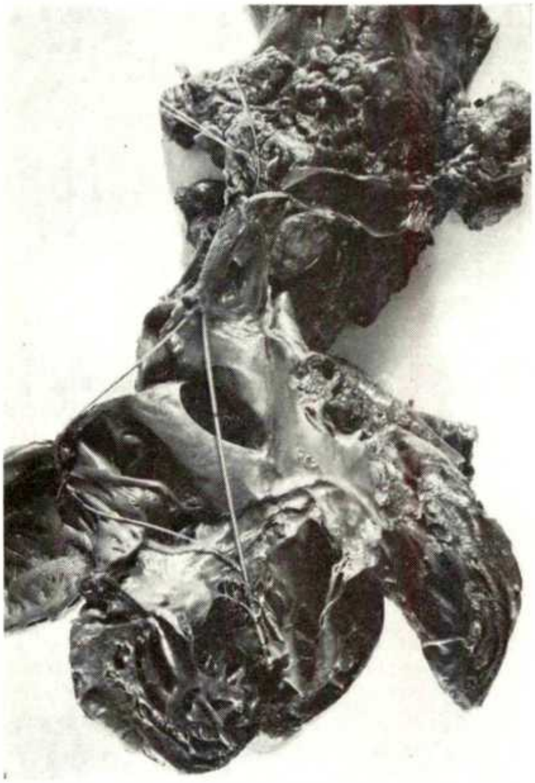

Fig. 1 *Two pacing electrodes are present in the right cavities, the smaller one (EMT 588) passing via the right innominate vein, the larger one (Sorin) via the left innominate vein. The large atrial septal defect is visible.*

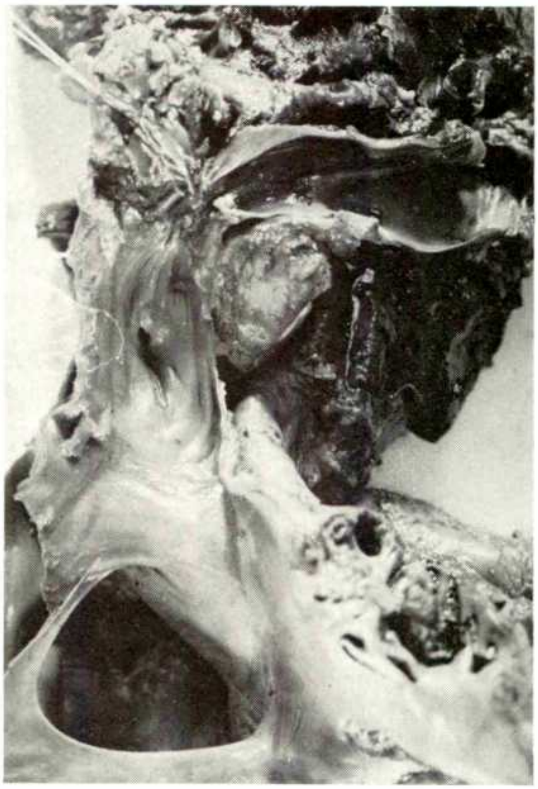

Fig. 2 *The superior vena cava has been cut open and the two electrodes have been removed. A severe stenosis of the venous lumen is visible at the intersection of the two electrodes at the junction of the innominate veins.*

which was also histologically examined, showed no evidence of organised thrombosis.

Discussion

Several cases of thrombosis around pacing electrodes have been reported (Lagergren *et al.*, 1966; Youmans *et al.*, 1967; Hager *et al.*, 1968; Prozan *et al.*, 1968; London *et al.*, 1969; Reynolds *et al.*, 1969; Robboy *et al.*, 1969; Sidd *et al.*, 1969; Griepp *et al.*, 1970; Kaulbach and Krukonis, 1970; Wertheimer *et al.*, 1973). To our knowledge only one case of superior vena cava syndrome in a pacemaker patient has been described (Wertheimer *et al.*, 1973). It occurred in a patient with two bipolar catheters and was successfully managed with oral anticoagulants. The case is somewhat similar to our patient, who also had two pacing electrodes. However, while the case described by Wertheimer, even in the absence of a postmortem study, was probably caused by thrombosis, in our patient, the picture is typical of venous stenosis at the intersection of the two catheters, with no evidence of thrombosis. This is consistent with the failure of anticoagulant and fibrinolytic therapy.

This complication of endocardial pacing is, in our opinion, favoured by the presence of two electrodes, especially if passing via veins of opposite sides, owing to irritation of the venous wall at the intersection. Such a complication, though rare at present, is, in our opinion bound to be seen more frequently with the growing number of patients with two or more pacing electrodes. Now that pacemaker circuits and energy sources have become more reliable, the electrode represents the weak point of the pacing system, as risk of a break is still high. However, we believe one should not resort to a second (or third) catheter implantation without careful consideration. A lead break in the subcutaneous tract or at the entrance of the vein, for instance, may often be repaired by suitable adaptors. Threshold problems may sometimes be managed by high energy pacemakers.

When implantation of a second electrode is absolutely necessary, we suggest the choice of a vein of the same side as that formerly used (e.g. the right jugular vein, when the first catheter has been inserted via the right cephalic), in order to avoid catheter crossing which may elicit fibrous tissue reaction and stenosis. Furthermore, one should always try to remove the old catheter, especially when, as in the case we have described, the tip is not anchored to the endocardium. When the old catheter is tightly fixed, as usually occurs, it may be worth while trying removal by weights.

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British Heart Journal, 1979, **42**, 490-492

Usefulness of Valsalva manoeuvre and cold pressor test for evaluation of arrhythmias in long QT syndrome[1]

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SUMMARY Ventricular arrhythmias were precipitated with reflex testing in a case of the long QT syndrome and were abolished after acute administration of propranolol.

Since the original description of a hereditary syndrome of prolongation of the electrocardiographic QT interval, syncope and sudden death, with congenital deafness (Jervell and Lange-Nielsen, 1957) or with normal hearing (Romano *et al.*, 1963; Ward, 1964), clinical evidence has accumulated to implicate the autonomic nervous system in the genesis of arrhythmia. The effects of catecholamine infusion (Garza *et al.*, 1970; Mathews *et al.*, 1972) and exercise (Roy *et al.*, 1976) have been reported to cause ventricular tachycardia and fibrillation in this syndrome. We tested the hypothesis that reflex manoeuvres would precipitate arrhythmias and found such testing useful for assessing the efficacy of antiarrhythmic therapy.

Case report

A 23-year-old white woman was referred to the University of California, San Francisco, for evaluation of recent postoperative arrhythmias. The patient was the product of a normal conception and delivery. During childhood she suffered 3 seizures and was treated with diphenylhydantoin until adolescence. She remained well until syncopal episodes occurred without warning during pregnancy: 1 episode during her first pregnancy and 2 during her second. For the past year she had been healthy, but was recently admitted to Alaska Hospital for minor pelvic surgery. Postoperatively she was noted to have frequent premature ventricular contractions, a potassium of 2·8 mmol/l, and a magnesium of 1·6 mmol/l. Potassium correction was undertaken and the patient transferred to the coronary care unit for monitoring. After transfer, short runs of ventricular tachycardia were noted. Treatment with bolus and infusion of lignocaine and procainamide was begun, together with an oral dose of quinidine. Runs of ventricular tachycardia occurred, followed by ventricular fibrillation. Cardiopulmonary resuscitation and praecordial electric shock restored normal rhythm. An electrocardiogram taken before cardiac arrest showed a QT interval of 0·46 second with a heart rate of 77. The calculated corrected QT (QTc) (Bazett, 1920) was prolonged to 0·52 second, with the upper limit of normal 0·425 second (Massie and Walsh, 1960). After treatment with bolus propranolol and supplemental potassium, the QT was 0·44 second at a heart rate of 71 (QTc = 0·48). There was an uneventful recovery. On the day of discharge, while on propranolol, 120 mg, and diphenylhydantoin, 300 mg, orally per day, she underwent progressive treadmill exercise with premature ventricular contractions at rest, which were abolished with exercise. Her dose of propranolol was subsequently increased to 160 mg per day. An audiogram was normal.

On admission she was a well-developed, well-nourished young woman in no acute distress. Vital signs, physical examination, and chest *x*-ray film were normal. Laboratory blood electrolyte values included a potassium of 4·0 mmol/l and a magnesium of 2·3 mmol/l. The electrocardiogram was normal, except for a QT of 0·48 second, with a heart rate of 55 (QTc = 0·46) at a time when the propranolol level was 200 ng/ml and the diphenyl-

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[1] This work was supported in part by an NHLBI Program Project Grant.

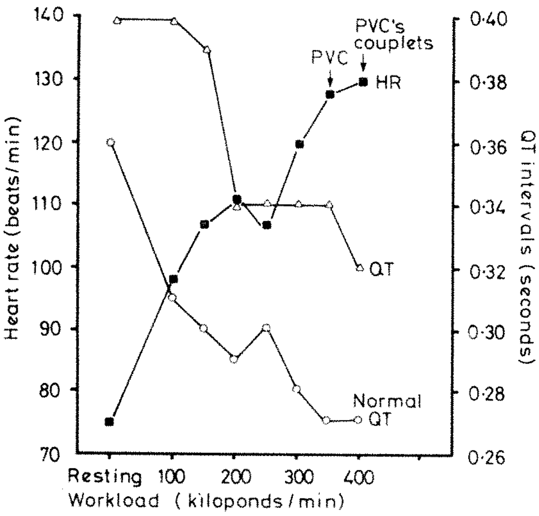

Fig. 1 *Heart rate and QT during exercise. Heart rate (solid squares) increased during exercise and was associated with premature ventricular contractions (PVC). QT interval (open triangles) was prolonged at rest and at exercise, compared with the upper limit of normal for QT corrected for heart rate (open circles).*

hydantoin level was 5 μg/ml. Her mother had been admitted to hospital for syncopal episodes with a reportedly normal QT interval; a brother had an electrocardiogram which showed right bundle-branch block; and a nephew had congenital unilateral deafness and motor difficulty.

HOSPITAL STUDIES

Exercise

All drugs, including antiarrhythmics, were stopped at least 24 hours before any studies. No arrhythmias were observed with the patient at rest during continuous monitoring.

In the cardiac catheterisation laboratory the patient underwent progressive supine bicycle exercise. The QT interval, which was prolonged at rest, showed progressive shortening with exercise, but nevertheless remained prolonged above normal (Fig. 1). At 400 kiloponds/min ventricular ectopy was manifested with coupled beats. Cardiac metabolism at rest and with exercise was normal, as judged from positive lactate extraction between coronary sinus and arterial blood.

Reflexes

The cold pressor test was performed with the hand immersed in ice water at 1°C. After 1 minute of immersion, ventricular bigeminy developed (Fig. 2). During Valsalva manoeuvre blowing, heart rate increased. With release, ventricular bigeminy occurred (Fig. 3). These studies were repeated after a 6 mg intravenous dose of propranolol. Heart rate response was diminished and no arrhythmias were observed. Each reflex manoeuvre was performed twice, both before and after propranolol. The results were the same each time.

In the past 6 months of outpatient follow-up, the patient has remained symptom and arrhythmia free on propranolol, 160 mg/day in divided doses.

Discussion

This case represents a potpourri of clinical features previously reported separately in the long QT interval syndrome. The early childhood 'seizures' were providentially treated with diphenylhydantoin, a drug said to shorten ventricular repolarisation (Bigger *et al.*, 1968). Further delay of syncopal episodes until young adult life is consistent with the previously reported onset of clinical manifestations

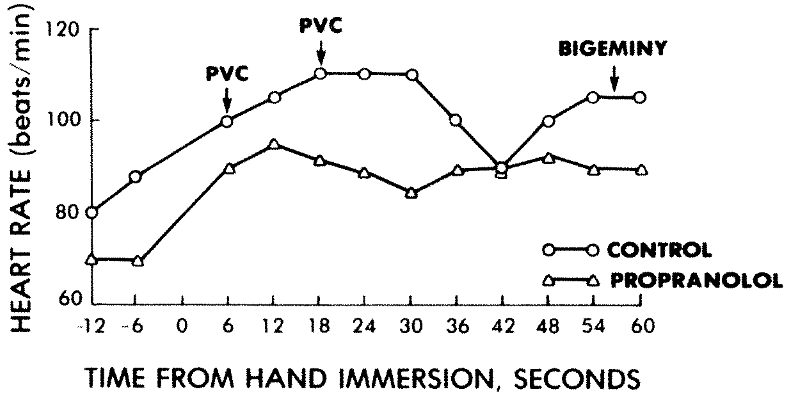

Fig. 2 *Cold pressor test. After hand immersion in ice water, premature ventricular contractions and ventricular bigeminy were noted. With beta-blockade, the increment of increase in heart rate was similar, but no ectopy occurred.*

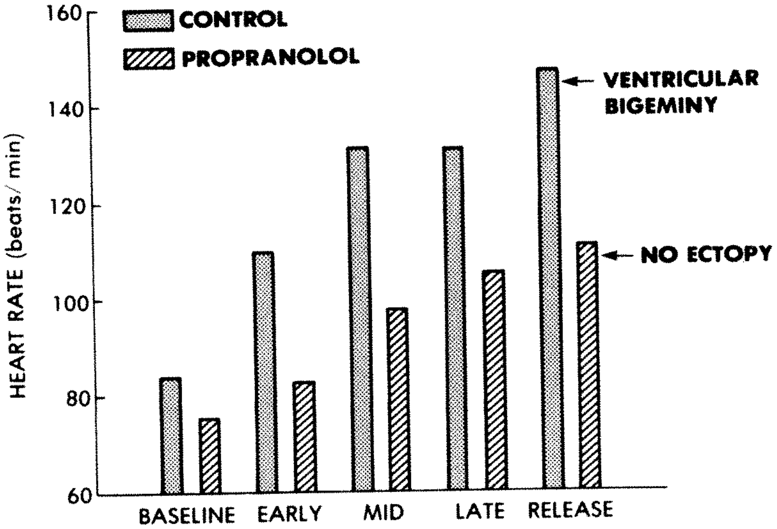

Fig. 3 *Valsalva manoeuvre. Heart rate rose during Valsalva manoeuvre and with release ventricular bigeminy occurred. After beta-blockade, repeat manoeuvre caused no ectopy.*

with variable age (Garza *et al.*, 1970; Mathews *et al.*, 1972; Roy *et al.*, 1976). The occurrence of severe arrhythmic episodes while in hospital for surgery may, in part, be attributed to stress in the postoperative period, as well as metabolic derangement. A single dose of quinidine was also administered and may have contributed to ventricular vulnerability (DiPalma and Shults, 1950).

The clinical evidence for a role of the sympathetic nervous system in the long QT syndrome includes precipitation of arrhythmias with exercise, emotional excitement, and catecholamine infusion and abolition of arrhythmias with beta-blockade (Jervell and Sivertssen, 1967; Garza *et al.*, 1970; Schwartz *et al.*, 1975; Roy *et al.*, 1976). After stellate ganglion blockade or left sympathectomy, shortening of the QT interval has been invoked as evidence for a disparity between sides of the stellate ganglion in sympathetic nervous system outflow to the ventricle (Schwartz *et al.*, 1975). In our patient, precipitation of ventricular arrhythmia with the Valsalva manoeuvre and a cold pressor test, and abolition of arrhythmia with propranolol, also provide examples of the precipitation of arrhythmias in the long QT syndrome by an action on the sympathetic chain. Our observation that propranolol abolished the ventricular arrhythmias associated with reflex manoeuvres and exercise is in agreement with the beta-blocking effect of this drug and at variance with the suggested direct antiarrhythmic effect (Garza *et al.*, 1970).

Although a recent review of drug therapy suggests the superiority of propranolol (Schwartz *et al.*, 1975), we encourage an individual approach in this serious malady. Using electrocardiographic monitoring, simple exercise testing and reflex manoeuvres may be useful to uncover ventricular ectopy and to assess drug therapy.

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British Heart Journal, 1979, **42**, 493-494

Electrical requirements of defibrillation

Sir,

In the November issue of the *British Heart Journal* in an editorial, Adgey (1978) discussed the subject of electrical requirements of ventricular defibrillation, and the controversy that exists about this subject. Almost all data are in agreement except those of the Purdue workers, Geddes *et al.* (1974) and Tacker *et al.* (1974).

In an attempt to verify the Tacker data we developed an automatic defibrillation measuring system, which will be reported elsewhere, and obtained the data presented in the Fig. The patients all had an acute coronary infarction, primary ventricular fibrillation, thus fibrillation not associated with cardiac failure. The results show that the clinical data of Crampton *et al.*, 1978 and Adgey *et al.*, 1978, and ourselves all indicate that with stored energies of 200 J or less a substantial number of patients can be defibrillated. The energy requirement as suggested by Tacker *et al.* (1974) is very different.

Since all reported clinical data seem to fit it seems imperative to study the Tacker data itself.

As stated by Lown in a personal communication to Adgey, reanalysing the Tacker clinical data did not show significant influence of body weight on success or failure of defibrillation. Thus, Tacker *et al.* might have misinterpreted their own clinical data.

We analysed the animal data as presented by Geddes *et al.* (1974). They used five different experimental species. Eight rabbits ranging in weight from 2·3 to 3·4 kg, 11 dogs 3·5 to 41 kg, 4 goats 29 to 39 kg, 10 ponies 80 to 193 kg, and 2 horses 277 to 340 kg.

It is unrealistic to assume that threshold data for those animals are comparable, for many reasons. One trivial reason is the fact that the shape of the thorax is different and therefore the distribution of the current in the thorax differs from species to species. Therefore the current density in the heart is different and also the threshold (Koning, 1972). For this reason we calculated from the Geddes data the power fit between current and energy, with respect to bodyweight for each species in the same

Rabbits	$I = 0{\cdot}46\ W^{2\cdot14}$ ($r = 0{\cdot}51$)	$U = 0{\cdot}24 W^{2\cdot71}$ ($r = 0{\cdot}35$)
	$I_{70} = 4085$ A	$U = 24{,}000$ J
	$I_{100} = 8765$ A	$U_{100} = 63{,}000$ J
Dogs	$I = 2{\cdot}7\ W^{0\cdot64}$ ($r = 0{\cdot}78$)	$U = 1{\cdot}62\ W^{1\cdot15}$ ($r = 0{\cdot}79$)
	$I_{70} = 41$ A	$U_{70} = 214$ J
	$I_{100} = 51$ A	$U_{100} = 323$ J
Goats	$I = 0{\cdot}74\ W^{1\cdot22}$ ($r = 0{\cdot}56$)	$U = 0{\cdot}02\ W^{2\cdot61}$ ($r = 0{\cdot}58$)
	$I_{70} = 132$ A	$U_{70} = 1486$ J
	$I_{100} = 204$ A	$U_{100} = 3811$ J
Ponies	$I = 8{\cdot}27\ W^{0\cdot55}$ ($r = 0{\cdot}55$)	$U = 0{\cdot}60\ W^{1\cdot56}$ ($r = 0{\cdot}65$)
	$I_{70} = 85$ A	$U_{70} = 453$ J
	$I_{100} = 104$ A	$U_{100} = 791$ J
Overall (Geddes)	$I = 1{\cdot}79\ W^{0\cdot88}$ ($r = 0{\cdot}94$)	$U = 0{\cdot}89\ W^{1\cdot48}$ ($r = 0{\cdot}94$)
	$I_{70} = 75$ A	$U_{70} = 479$ J
	$I_{100} = 103$ A	$U_{100} = 812$ J

I = current strength, U = energy, W = bodyweight (kg), r = correlation coefficient.

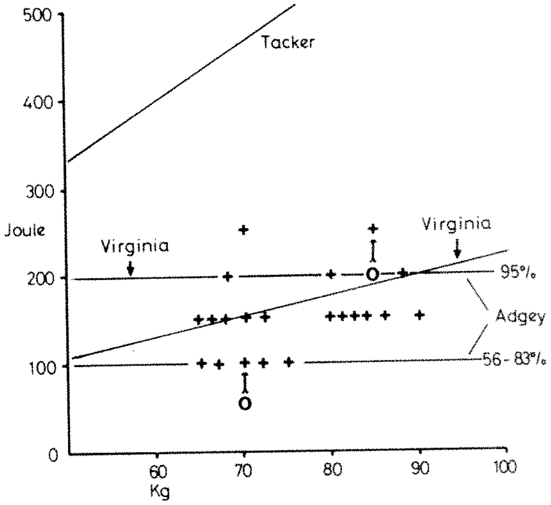

Fig. *Energy levels for human defibrillation as a function of bodyweight. Both Adgey and Virginia data represent a percentage success with the used level of energy. A successful event in our study is indicated with a plus and a failure with a zero. The dose suggested by Tacker* et al. *(1974) is also indicated. Data obtained in co-operation with Dr Nanninga, Department of Cardiology, Sittard, the Netherlands. The Virginia data as presented by the regression line are for 100 per cent success in the coronary patient.*

way as Geddes did for all species. From the computed relations we calculated the current and energy for a 70 and 100 kg subject of the same species (see Table).

Our conclusions from the recomputed Geddes animal data are:

(1) The different species all have different relations between energy and current with respect to body weight.

(2) Those relations are very weak because correlation coefficients ranged from 0·35 to 0·79; this makes extrapolation to higher bodyweight hazardous, and this is emphasised by the rabbit and goat data extrapolated to large weights.

(3) The difference in the mentioned relation between different species makes extrapolation to humans untenable.

(4) The clinical dose as recommended by Geddes and Tacker is based on weak experimental data. Therefore it seems logical that their dose differs from the actual one measured in clinical practice.

Finally we suggest that there need not be a controversy about defibrillation requirements, because the only conflicting data are based on weak grounds.

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British Heart Journal, 1979, **42,** 495-496

Hypothesis for low-energy transthoracic defibrillation

Sir,
The editorial on ventricular defibrillation (Adgey, *British Heart Journal,* 1978, **40,** 1197–1199) is both timely and informative. The Belfast group has a prodigious experience in out-of-hospital resuscitation and their prospectively collected data have been invaluable in determining energy requirements for defibrillation. The evidence indicating the need for defibrillators storing more than 400 Ws is, at present, inadequate and unconvincing (Lown *et al.,* 1978).

In addition to the views expressed by Dr Adgey, I would like to submit some theoretical considerations which may help to explain the surprising efficacy of low energy shocks. The proponents of high energy defibrillation espouse the view that as body weight increases, the energy required to defibrillate increases, presumably, in a fixed mathematical manner. They have suggested that a log-dose-response curve based on body weight exists for ventricular defibrillation (Geddes *et al.,* 1974; Tacker *et al.,* 1974). This argument presumably presupposes, as did Wiggers in 1940, that complete depolarisation of the heart is necessary to terminate ventricular fibrillation. Though the animal studies are convincing, it is not clear that such a condition needs to be met to effect defibrillation clinically.

Evidence of the latter view derives from more recent studies involving intracavitary catheter defibrillation studies in animals and in man (Mirowski *et al.,* 1973; Ewy *et al.,* 1978). In this model, energies as low as 4 Ws may terminate ventricular fibrillation. It is extremely unlikely that such low energies are capable of depolarising the entire myocardium. Zipes *et al.* (1975) have also shown that selective infusion of potassium chloride into coronary arteries can also terminate ventricular fibrillation. They postulated that segmental depolarisation of the myocardium occurs with such selective infusions. It is likely that, with both methods, a critical mass of myocardium is temporarily disengaged by depolarisation from the remainder of the fibrillating heart. This effect is evidently adequate to abort ventricular fibrillation as the multiple re-entering wavefronts encounter either refractory or partially refractory tissue. There is no basis for making an *a priori* assumption that this effect relates to body weight. Even if body weight or heart weight were a factor, it may be expected that much lower energies than are required to depolarise the entire heart would suffice to defibrillate it. If a similar mechanism operates during transthoracic defibrillation, it would account for the success of low-energy defibrillation.

In view of the clinical data provided by the Belfast (Pantridge *et al.,* 1975; Campbell *et al.,* 1977) and the Virginia (Crampton and Hunter, 1976; Gascho *et al.,* 1979) groups, it is necessary to evaluate critically the reasons for failure during defibrillation. It is likely that the most egregious miscreant is the user and not the device. It is distressing to see how frequently electrodes are malpositioned on the chest during defibrillation. It was, I believe, Dr Samuel Johnson's acerbic wit which informed us, in another connection, that a cigarette, 'is a device with a fire at one end and a fool at the other'. Each improper discharge of the defibrillator provides an opportunity to paraphrase this redoubtable sage.

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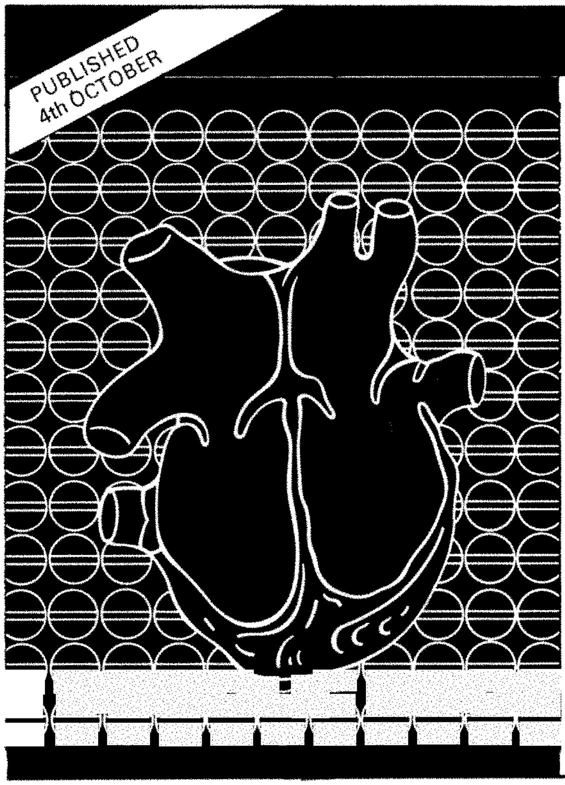

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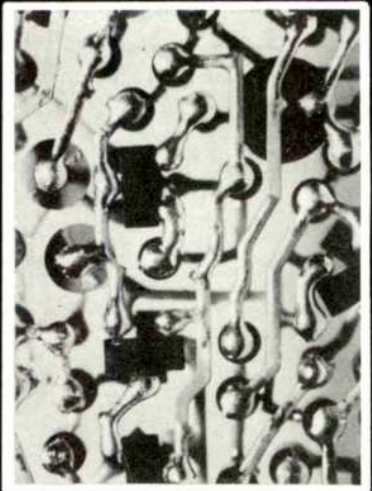

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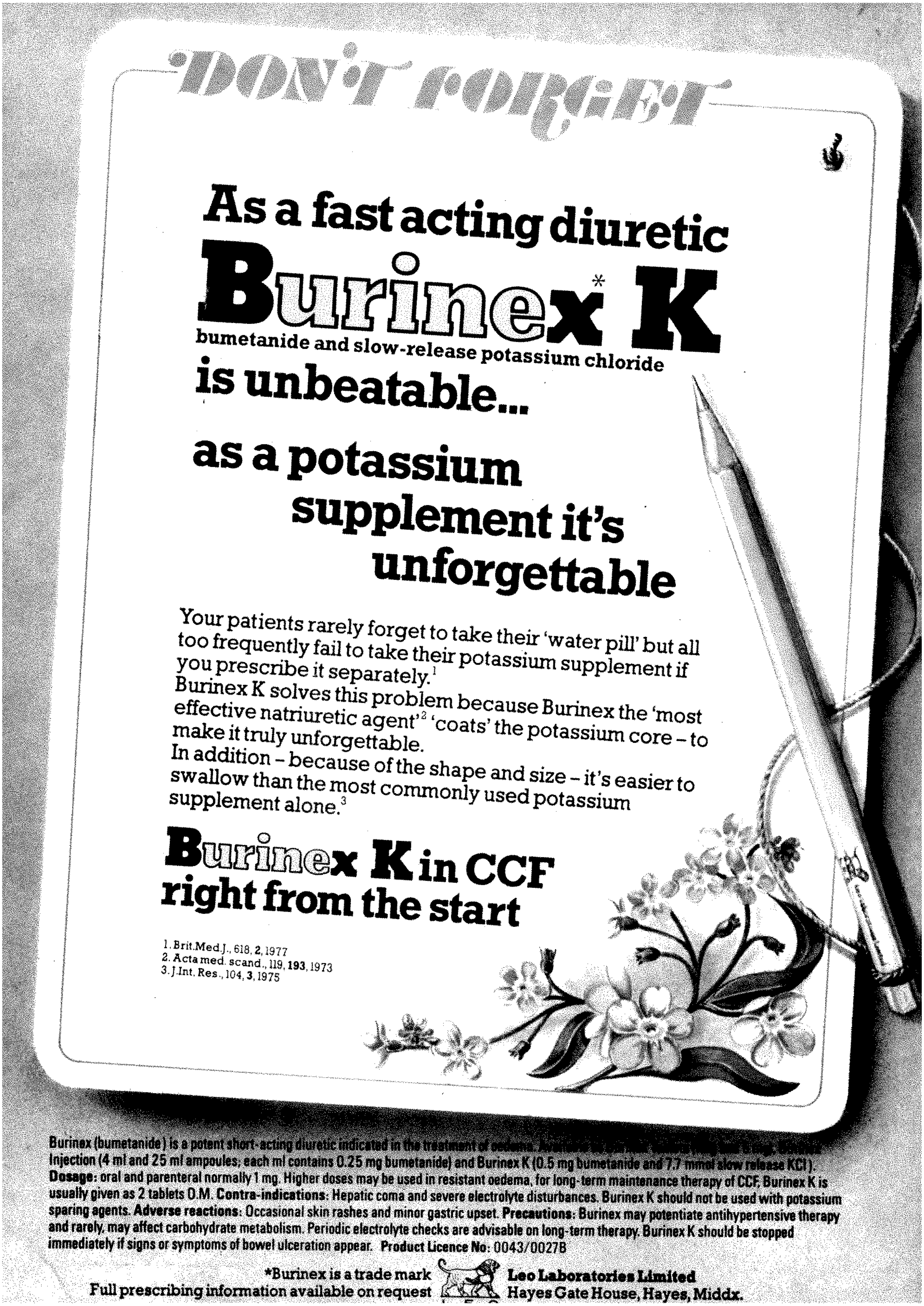

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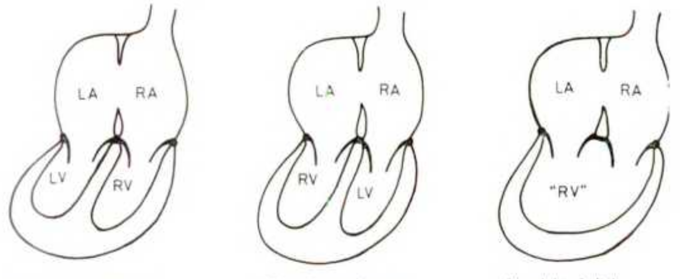


AV concordance
5 cases

AV discordance
4 cases

Double inlet
2 cases
("RV type")

Fig. 4 *Diagram illustrating atrioventricular connections in situs inversus. Abbreviations as for Fig. 3.*

the right in four cases, anterior and to the left in three, posterior and to the left in one, and posterior in one.

Aortic arch

The aortic arch was right sided in eight patients (73%) and left sided in three (27%).

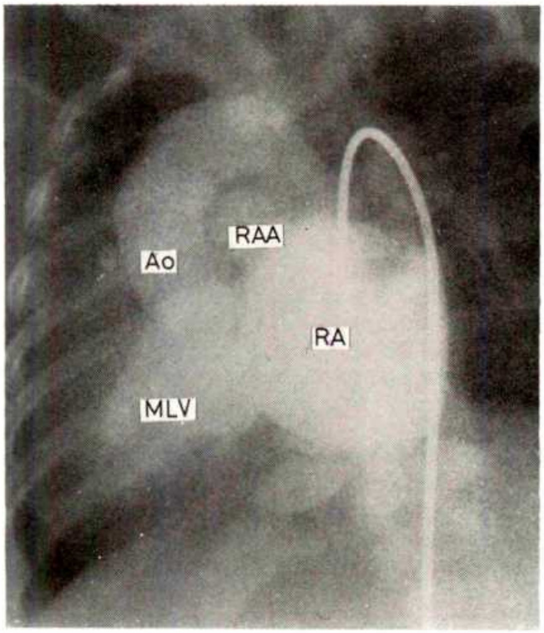


Fig. 5 *Angiocardiogram (injection into right atrium) of patient with situs inversus, atrioventricular discordance, and ventriculoarterial concordance viewed in anteroposterior projection. At operation for atrial septectomy aorta was found to be posterior and to right of pulmonary artery. The chamber connections deduced from the angiocardiogram were confirmed. Note also morphologically right atrial appendage (RAA) juxtaposed behind pulmonary artery (not seen) and catheter entering right atrium via azygos continuation of inferior vena cava. RA, right atrium (left sided); MLV, morphologically left ventricle; Ao, aorta.*

Associated anomalies

Pulmonary stenosis and ventricular septal defect were the commonest lesions. The patient with discordant atrioventricular connections and concordant ventriculoarterial connections (isolated atrial inversion) had right juxtaposition of the atrial appendages with azygos continuation of the inferior vena cava to the left superior vena cava (Fig. 5).

SITUS AMBIGUUS, LAEVOISOMERISM

In four patients atrial laevoisomerism was suggested by the bronchial anatomy on the chest x-ray film, confirmed by necropsy in one (Fig. 6). In two of these patients the liver was central (visceral situs ambiguus) but in two the liver was right sided (visceral situs solitus).

Atrioventricular junction (Fig. 7)

Three patients had two ventricles and one a univentricular heart of indeterminate type (without rudimentary chamber). In the biventricular hearts the right ventricle was to the right in one case and to the left in two cases.

The mode of connection was through a common atrioventricular valve in three cases and via two perforate atrioventricular valves in one case.

Arterial junction

Of three patients with two ventricles, one had concordant ventriculoarterial connection, one double outlet right ventricle, and one single outlet (truncus arteriosus). The remaining patient had double outlet from the sole indeterminate ventricular chamber.

The aorta was anterior and to the right in one case, anterior and to the left in one case, and to the left in one case. The remaining case had a truncus with the aortic component posterior to the pulmonary component.

Aortic arch

The aortic arch was left sided in three patients and right sided in one.

Aortic arch	*Associated anomalies*	*Visceral situs*	*Thoracic situs*
Right	Ventricular septal defect	Solitus	Solitus
Left	Ascending aorta gives R-L pulmonary arteries; ductus—descending aorta	Solitus	Solitus
Left	Ventricular septal defect; pulmonary stenosis	Solitus	Solitus
Left	Ventricular septal defect	Solitus	Solitus
Left	Ventricular septal defect; pulmonary stenosis	Solitus	Solitus
Left	Ventricular septal defect; persistent ductus arteriosus	Solitus	Solitus
Right	Persistent ductus arteriosus	Solitus	Solitus
Right		Solitus	Solitus
ight	Persistent ductus arteriosus	Solitus	Solitus
eft	Pulmonary stenosis	Solitus	Solitus
eft	Atrial septal defect; pulmonary stenosis	Solitus	Solitus
ight	Left juxtaposition of atrial appendages; pulmonary stenosis	Solitus	Solitus
eft	Left juxtaposition of atrial appendages	Solitus	Solitus
eft	Patent foramen ovale; persistent ductus arteriosus	Solitus	Solitus
eft	Severe pulmonary stenosis	Solitus	Solitus
eft	Persistent ductus arteriosus	Solitus	Solitus
ight	Aneurysm of membranous septum	Inversus	Inversus
eft	Severe pulmonary stenosis	Inversus	Inversus
ight		Inversus	Inversus
eft	Supulmonary stenosis; persistent ductus arteriosus	Inversus	Inversus
eft	PDA; VSD; left SVC	Inversus	Inversus
ight	ASD; right juxtaposition of atrial appendages; left IVC-azygos-left SVC	Inversus	Inversus
ght	Ventricular septal defect	Inversus	Inversus
ght	Pulmonary stenosis	Inversus	Inversus
ght	Right SVC; ASD	Inversus	Inversus
ght	Severe pulmonary stenosis	Inversus	Inversus
ght	Pulmonary stenosis	Inversus	Inversus
ght	VSD; ASD; severe PS; left juxtapostion of atrial appendages	Right liver, left stomach	L ambiguus
eft	Left IVC—azygos—left SVC	Midline liver, left stomach	L ambiguus
eft	Right IVC—azygos—right SVC	Right liver, left stomach	L ambiguus
eft	Subaortic stenosis; right IVC—azygos—right SVC	Midline liver, left stomach	L ambiguus
eft	Bilateral SVC; right IVC receives R and L inferior pulmonary veins	Asplenia, midline liver, left stomach	R ambiguus
eft	Persistent ductus arteriosus	Asplenia, left-midline liver, left stomach	R ambiguus

bited discordant arterial connections and the other of left ventricular type had double outlet main chamber. One of the univentricular hearts of right ventricular type had double outlet main chamber, the other two having single outlet with pulmonary atresia. Of the univentricular hearts of indeterminate type, two had double outlet and the other single outlet with pulmonary atresia.

Aortic arch

The aortic arch was left sided in 11 patients (70%) and right sided in five (30%).

Associated anomalies

Persistent ductus arteriosus, ventricular septal defect, and pulmonary stenosis were the commonest anomalies. Two patients had left juxtaposition of the atrial appendages.

SITUS INVERSUS

In all cases we found visceral, thoracic, and atrial situs to correspond.

Atrioventricular junction (Fig. 4)

Eleven patients had situs inversus, of whom five had concordant and four discordant atrioventricular connections. The remaining two patients had double inlet ventricles, in both of which the ventricular morphology was of a univentricular heart of right ventricular type with a posterior right-sided trabecular pouch of left ventricular type.

The right ventricle, in the nine cases with two ventricular chambers, was to the left of the left ventricle in five (all with concordant atrioventricular connections) and to the right in four (with discordant atrioventricular connections).

Arterial junction

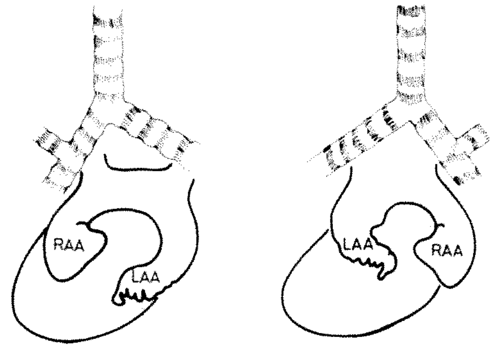
The ventriculoarterial connection in the five patients with concordant atrioventricular connections was concordant in one, double outlet right ventricle in three, and single outlet in the other (aorta with pulmonary atresia). Of the four patients who had discordant atrioventricular connections, one had concordant ventriculoarterial connections (Fig. 5). This chamber arrangement has been termed 'isolated atrial inversion' by other workers (Clarkson *et al.*, 1972), and was confirmed at operation in our case. Of the remaining patients, two had discordant ventriculoarterial connections and one double outlet right ventricle. In both the patients with univentricular hearts the arterial connection was double outlet from the main chamber.

In the group as a whole the aorta was anterior to the pulmonary artery in two cases, anterior and to

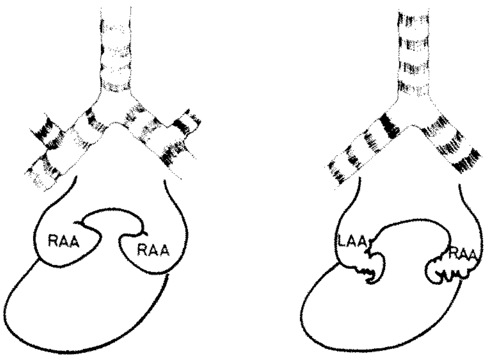
Table *Distribution and anatomy of patients studied; every heart was analysed in terms of connections, relations, and morphology (see text)*

Case no.	*Atrial situs*	*AV junction* *AV connection*	*Mode of connection*	*Ventricular morphology*	*Relation of ventricles and of rudimentary to main chamber*	*Arterial junction* *Arterial connection*	*Relation of arteries*	*Infundibular morphology*
1	Solitus	Concordant	2 AV valves	2 ventricles	RV superior to LV	Concordant	AR	Subpulmonary
2	Solitus	Concordant	2 AV valves	2 ventricles	RV to right of LV and anterior	Single outlet truncus		Mitral-truncal continuity
3	Solitus	Discordant	2 AV valves	2 ventricles	RV to left of LV and anterior	Discordant	AL	Subaortic
4	Solitus	Discordant	2 AV valves	2 ventricles	RV to left of LV and anterior	DORV	A	Bilateral
5	Solitus	Discordant	2 AV valves	2 ventricles	RV to left of LV and anterior	DORV	AL side-by-side	Bilateral
6	Solitus	Discordant	2 AV valves	2 ventricles	RV to left of LV and anterior	DORV	AL side-by-side	Bilateral
7	Solitus	Double inlet	R AV valve straddling	UV heart LV type	OC to right of MC and anterior	Concordant	RP	Subaortic
8	Solitus	Double inlet	Common AV valve	UV heart LV type	Pouch to right of MC	Double outlet	A	Subaortic
9	Solitus	Double inlet	L AV valve hypoplastic	UV heart RV type	Pouch posterior to MC	Single outlet-aorta; pulmonary atresia	A	Subaortic
10	Solitus	Double inlet	2 AV valves	UV heart indeterminate type	No rudimentary chamber	Double outlet	A	Subaortic
11	Solitus	Absent R AV connection		UV heart LV type	OC anterior to MC	Discordant	A	Subaortic
12	Solitus	Absent R AV connection		UV heart LV type	OC to right of MC and anterior	Discordant	A R	Subaortic
13	Solitus	Absent R AV connection		UV heart RV type	Pouch to right of MC and posterior	Double outlet	A R	Subaortic
14	Solitus	Absent R AV connection		UV heart RV type	Pouch to right of MC and posterior	Single outlet-aorta; pulmonary atresia	A	Bilateral
15	Solitus	Absent R AV connection		UV heart indeterminate type	No rudimentary chamber	Double outlet	A L	Subaortic
16	Solitus	Absent R AV connection		UV heart indeterminate type	No rudimentary chamber	Single outlet-aorta; pulmonary atresia		Bilateral
17	Inversus	Concordant	2 AV valves	2 ventricles	RV anterior and left of LV	Concordant	P L	Subpulmonary
18	Inversus	Concordant	2 AV valves	2 ventricles	RV anterior and left of LV	DORV	A L	Bilateral
19	Inversus	Concordant	2 AV valves	2 ventricles	RV anterior and left of LV	DORV	A L	Bilateral
20	Inversus	Concordant	2 AV valves	2 ventricles	RV anterior and left of LV	DORV	A L	Bilateral
21	Inversus	Concordant	2 AV valves	2 ventricles	RV to left of LV	Single outlet-aorta; pulmonary atresia	A R	Subaortic
22	Inversus	Discordant	2 AV valves	2 ventricles	RV to right of LV and posterior	Concordant	P	Subpulmonary
23	Inversus	Discordant	2 AV valves	2 ventricles	RV to right of LV and posterior	Discordant	A R	Subaortic
24	Inversus	Discordant	2 AV valves	2 ventricles	RV to right of LV and posterior	Discordant	A R	Subaortic
25	Inversus	Discordant	2 AV valves	2 ventricles	RV anterior and superior to LV	DORV	A	Bilateral
26	Inversus	Double inlet	2 AV valves	UV heart RV type	Pouch posterior to MC	Double outlet	A	Subaortic
27	Inversus	Double inlet	Common AV valve	UV heart RV type	Pouch to left of MC	Double outlet	A R	Subaortic
28	L ambiguus	Ambiguus	2 AV valves	2 ventricles	RV posterior to LV	Concordant	P	Bilateral
29	L ambiguus	Ambiguus	Common AV valve	2 ventricles	RV to left of LV	DORV	A R side-by-side	Bilateral
30	L ambiguus	Ambiguus	Common AV valve	2 ventricles	RV to left of LV and anterior	Single outlet-truncus		Mitral-truncal continuity
31	L ambiguus	Double inlet	Common AV valve	UV heart indeterminate type	No rudimentary chamber	Double outlet	A L	Subaortic
32	R ambiguus	Ambiguus	Common AV valve	2 ventricles	RV to left of LV and anterior	DORV	A	Bilateral
33	R ambiguus	Double inlet	Common AV valve	UV heart LV type	OC to left of MC and anterior	Single outlet-aorta; pulmonary atresia	A L	Subaortic

Abbreviations: AV, atrioventricular; A, anterior; R, right; P, posterior; L, left; UV, univentricular; RV, right ventricle; LV, left ventricle; DORV, double outlet right ventricle; PS, pulmonary stenosis; VSD, ventricular septal defect; ASD, atrial septal defect; IVC, inferior vena cava; SVC, superior vena cava; MC, main chamber; OC, outlet chamber



Solitus - 16 cases Inversus - 11 cases



Ambiguus with dextro isomerism - 2 cases

Ambiguus with laevo isomerism - 4 cases

Fig. 2 *Diagram illustrating bronchial anatomy. RAA, right atrial appendage; LAA, left atrial appendage.*

univentricular hearts, six with absent right atrioventricular connection and four with double inlet connections.

Of the 10 patients with univentricular hearts, four had univentricular hearts of left ventricular type, two with double inlet and two with absent right atrioventricular connection. Three patients had univentricular hearts of right ventricular type, two with absent right connection and one with double inlet, while three had univentricular hearts of indeterminate type, one with double inlet and two with absent right atrioventricular connection (Fig. 3). The seven univentricular hearts of right or left ventricular type all possessed rudimentary chambers, four of which were outlet chambers giving rise to a great artery while three were trabecular pouches, having neither inlet nor outlet portions.

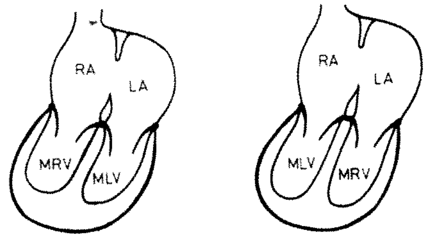
The right ventricle was to the right of the left ventricle in one of the six patients with two ventricles (concordant atrioventricular connection), to the left in four (discordant atrioventricular connections), and anterosuperior to the left ventricle in one (concordant atrioventricular connections).

Arterial junction

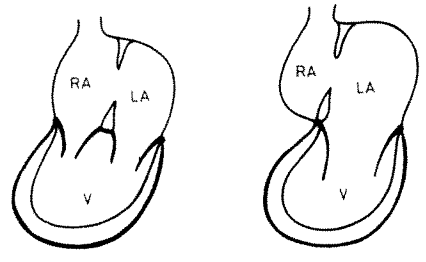
One of the two patients with concordant atrioventricular connections had concordant ventriculo-arterial connections, the aorta being anterior and to the right of the pulmonary artery. The other had a truncus arteriosus with a right-sided origin of the pulmonary trunk.

Of the four patients with discordant atrioventricular connections, the arterial connections were discordant in one, the aorta being anterior and to the left, and double outlet right ventricle in three. In the latter cases the aorta was anterior and to the left in two and directly anterior in one; all had bilateral infundibula.

Of the 10 patients with univentricular heart, only one, with a main chamber of left ventricular type, had concordant arterial connections. Two univentricular hearts of left ventricular type exhi-



AV Concordance - 2 cases AV Discordance - 4 cases



Double inlet ventricle
4 cases

Ventricle -	LV type	2
	RV type	1
	Indeterminate	1

Absent Rt connection
6 cases

Ventricle -	LV type	2
	RV type	2
	Indeterminate	2

Fig. 3 *Diagram illustrating atrioventricular connections found in cases with situs solitus. RA, right atrium; LA, left atrium; MRV, morphologically right ventricle; MLV, morphologically left ventricle; V, ventricle in univentricular heart; AV, atrioventricular; Rt, right.*

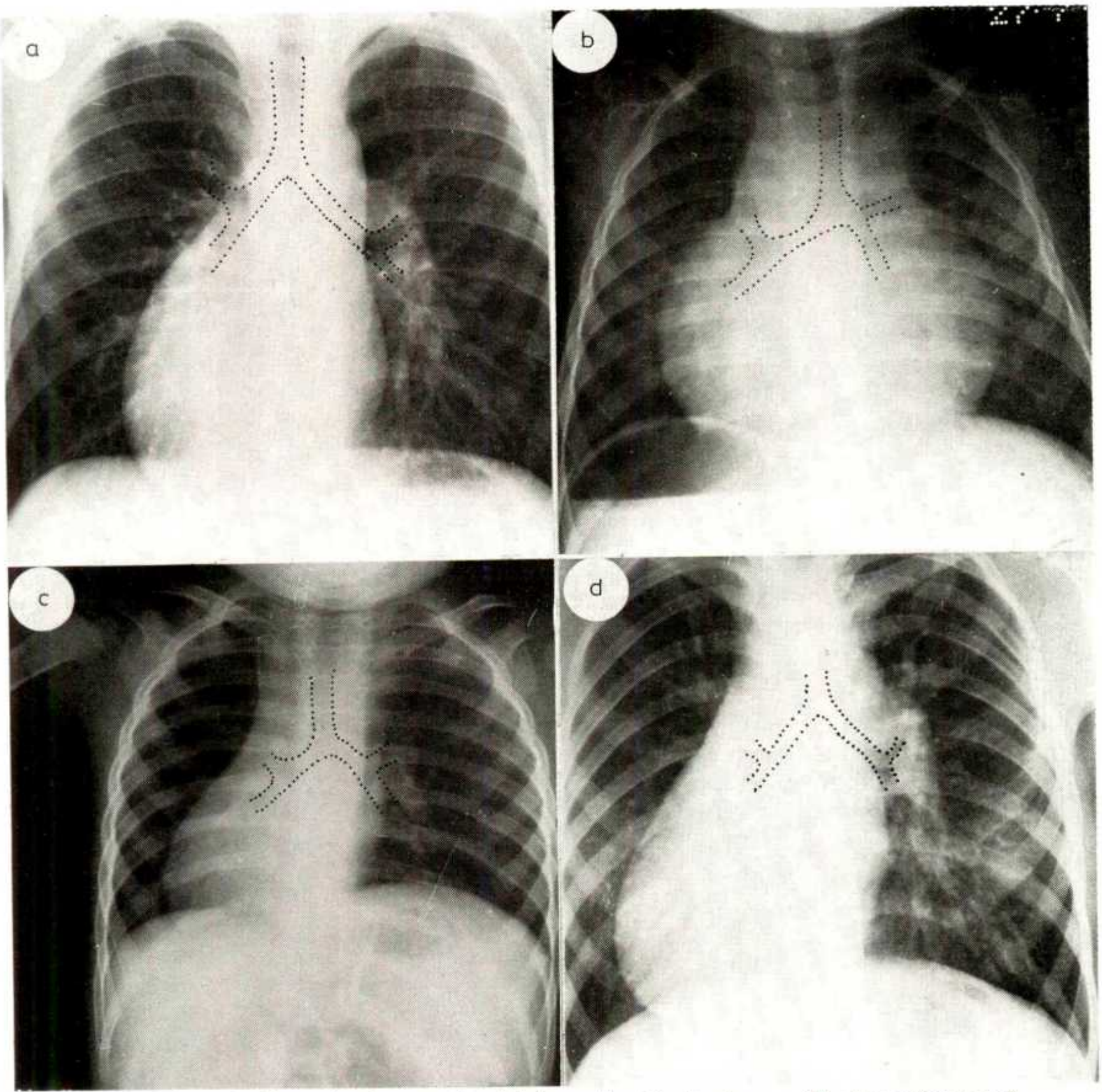


Fig. 1 *Chest radiographs illustrating dextrocardia with situs solitus* (a), *situs inversus* (b), *situs ambiguus with dextroisomerism* (c), *and with laevoisomerism* (d). *Situs was judged from bronchial anatomy which was easily visible on radiographs. It is less obvious on prints and position of bronchi is indicated by dotted lines.*

this report. Each of these patients was analysed in terms of connections, relations, and morphology using the system described elsewhere in detail (Tynan *et al.*, 1979).

Findings

The anatomy of the hearts in the patients studied is shown in the Table. There were 16 patients with situs solitus (48%), 11 (33%) with situs inversus, and six (18%) with situs ambiguus (Fig. 2). Four of the cases of situs ambiguus exhibited laevoisomerism, and two dextroisomerism.

SITUS SOLITUS

In all patients we found visceral, thoracic, and atrial situs to correspond.

Atrioventricular junction (Fig. 3)

Of 16 patients with situs solitus, two had concordant and four discordant atrioventricular connections. The remaining 10 patients had

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Dextrocardia—value of segmental analysis in its categorisation

GIUSEPPE CALCATERRA[1], ROBERT H. ANDERSON[2], KAI C. LAU[3], AND ELLIOT A. SHINEBOURNE

From the Department of Paediatrics, Cardiothoracic Institute, Brompton Hospital, London

SUMMARY Dextrocardia can be defined as a heart in the right chest with the major axis to the right. This definition, however, conveys no information regarding the chamber arrangements and internal anatomy of the heart.

Of 40 patients satisfying this definition in the files of the Brompton Hospital, 33 had angiocardiographic data adequate for complete analysis in terms of connections, relations, and morphology of cardiac segments. They form the subject of this report.

There were 16 (48%) patients with situs solitus, 11 (33%) with situs inversus, and six (18%) with situs ambiguus. Of the cases of situs ambiguus, four exhibited laevoisomerism and two dextroisomerism. Of the 16 patients with situs solitus, six had two ventricles and 10 had univentricular hearts; two patients had concordant and three discordant ventriculoarterial connections, seven had double outlet ventricle, and four a single outlet heart. Of the 11 patients with situs inversus, nine had two ventricles and two a univentricular heart of right ventricular type; the arterial connection was concordant in two, discordant in two, double outlet in six, and single outlet in one. Of the six patients with situs ambiguus and laevo or dextroisomerism, four had two ventricles, and two univentricular hearts; the arterial connection was concordant in one, double outlet in three, and single outlet in two.

Segmental analysis and the use of basic descriptive terms are essential to define the complex anatomy of such hearts.

The term dextrocardia is used by some authors (Van Praagh *et al.*, 1964; Van Praagh and Vlad, 1978) to describe the situation where on plain chest *x*-ray the heart is predominantly in the right hemithorax. Others use the term to describe the situation where the apex or major axis of the heart (Lev *et al.*, 1968; Squarcia *et al.*, 1973) points to the right. As a right-sided position of the heart has no implications for the internal anatomy, controversy about the precise definition or use of the term dextrocardia, or such terms as dextroposition, dextroversion, dextrorotation, or dextrotorsion, is unhelpful. As Van Praagh and colleagues (1964) and Squarcia *et al.* (1973) have shown, segmental analysis is essential for complete description of such hearts. In this paper we describe an analysis of cases from the Brompton Hospital, fulfilling these definitions for dextrocardia, but have used a system of analysis which distinguishes the connections of the cardiac chambers and great arteries from their spatial interrelations (Shinebourne *et al.*, 1976) and which, in addition, describes abnormal morphology without resort to embryological considerations (Tynan *et al.*, 1979).

Patients studied

We have analysed the radiographic, angiographic, and, where appropriate, necropsy data in 40 patients on file at the Brompton Hospital as having their hearts within the right hemithorax, with the major cardiac axis pointing to the right (Fig. 1). The radiographic examination was particularly important since from it information was derived about the disposition of the bronchi and abdominal viscera which permitted the determination of atrial situs, vital knowledge in the analysis of patients with dextrocardia.

In only 33 were the data adequate for definitive and complete analysis and they form the subject of

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[1] Visiting Fellow from Ospedale Maggiore della Carita, Novara, Italy.
[2] Supported by the Joseph Levy Foundation and the British Heart Foundation.
[3] Heinz Fellow, British Paediatric Association.

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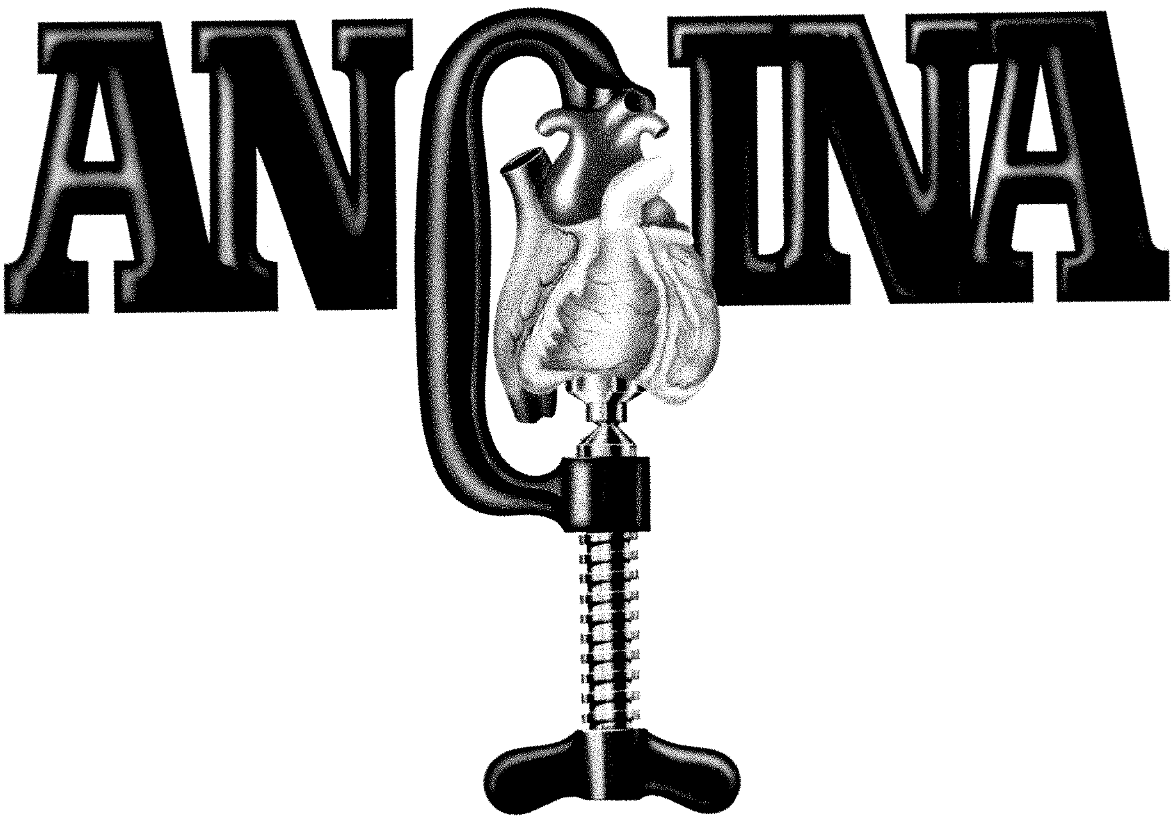

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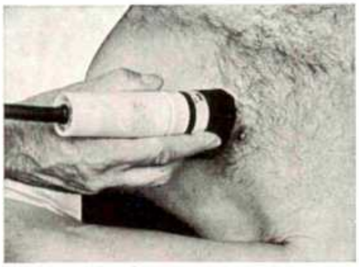

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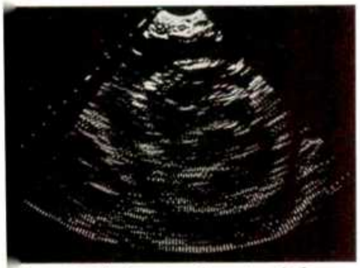

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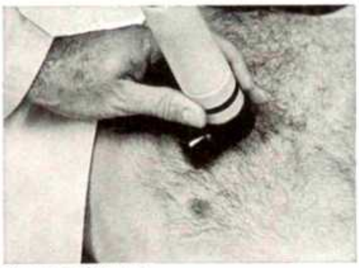

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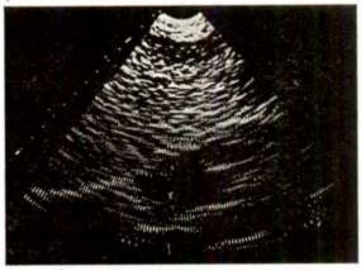
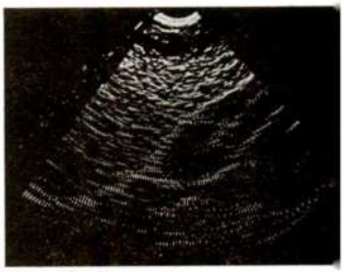
Pericardial effusion.

Inferior Vena Cava entering right atrium.



Normal



Tricuspid valve vegetation.

Small pericardial effusion, long axis view.

Pericardial effusion, short axis view.

Tricuspid valve vegetation.

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1789

The discovery of animal electricity

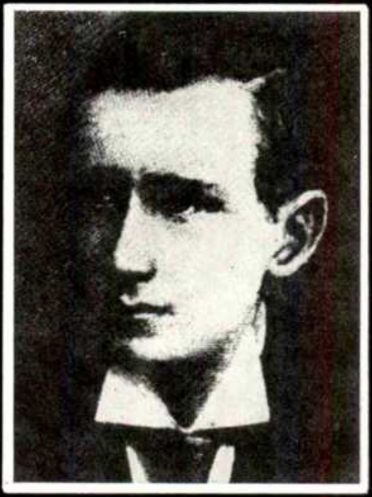
Luigi Galvani
(Bologna 1737-1798)

The discovery of electricity in animals is owed to this man. He made interesting observations on birds' renal secretion and on the inhibiting action of the vagus nerve on the heart.

Bologna

1901

The first radio signal to cross the Atlantic



Guglielmo Marconi
(Bologna 1874-Roma 1937)

He is universally known for the invention of wireless telegraphy which served as the basis for research in radiophonic broadcasting. In 1909 he received the Nobel Prize for physics.

Bologna

1978

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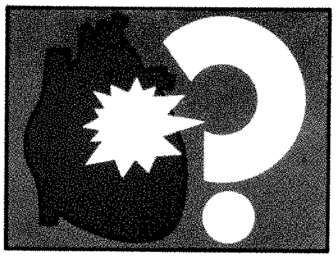
BRITISH HEART JOURNAL

MYOCARDIAL INFARCTION?



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Where E.C.G., case history and total enzyme measurements leave a margin of doubt, the information provided by CK and LDH isoenzyme testing is unequivocal, allowing you to state with total confidence whether or not myocardial infarction has occurred.

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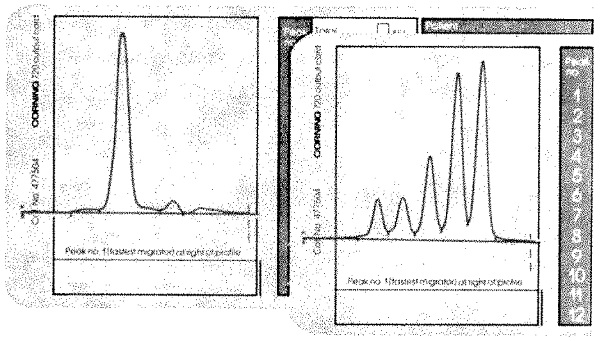
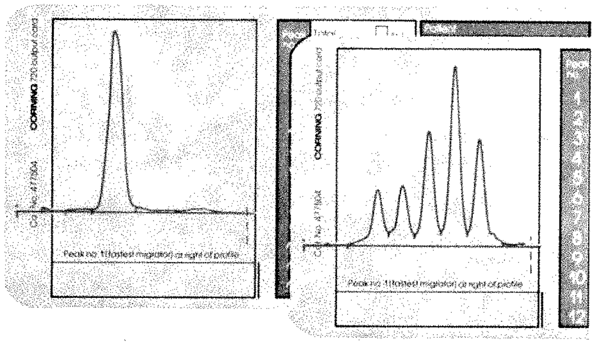


This patient *has* had a myocardial infarction.



This patient has *not* had a myocardial infarction.

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THE X-RAY DIAGNOSIS OF CONGENITAL HEART DISEASE IN INFANTS, CHILDREN, AND ADULTS: Pathologic, Hemodynamic, and Clinical Correlations as Related to the Chest Film (2nd Ed.) *by* **Larry P. Elliott,** *Univ. of Alabama School of Medicine, Birmingham, Alabama, and* **Gerold L. Schiebler,** *Univ. of Florida College of Medicine, Gainesville, Florida.* This new edition features data on complex congenital heart disease, analysis of cyanotic heart disease chest films, hypertension, pulmonary stenosis, and related topics. *'79, 448 pp. (6 3/4 x 9 3/4), 405 il., 13 tables, $36.50*

EXERCISE AND CORONARY HEART DISEASE: Role in Prevention, Diagnosis, Treatment (2nd Ed.) *by* **Gerald F. Fletcher** *and* **John D. Cantwell,** *both of Georgia Baptist Hospital, Atlanta, Georgia.* Practical and informative guidelines to the full rehabilitation of the coronary heart disease patient are featured. Interaction of exercise with various risk factors, directions for exercise training, specific in-hospital and outpatient exercise regimens, and the potential dangers of exercise are among the subjects discussed. *'79, 352 pp., 85 il., 24 tables, $27.50*

A PICTORIAL HISTORY OF MEDICINE (5th Ptg.) *by* **Otto L. Bettmann,** *The Bettmann Archive, New York, New York. Foreword by* **Philip S. Hench.** This pictorial history of medicine covers a time span which ranges from early Egyptian and ancient Eastern cultures through civilizations of the Nineteenth Century. A compact pictorial unit of each medical landmark offers the reader a technical and cultural perspective. *'79, 336 pp. (8 1/2 x 11), 1000 il., $14.50, paper*

DIABETES AND THE HEART *edited by* **Samuel Zoneraich,** *State Univ. of New York, Stony Brook, New York. (27 Contributors)* Renowned authorities from a number of disciplines explore a variety of topics related to diabetes and the heart. Coronary artery disease, the cardiomyopathies, noninvasive diagnostic tests, the use of drugs, the concomitant use of alcohol and insulin, and systemic metabolic responses during acute myocardial infarction are among the subjects reviewed. *'78, 320 pp. (6 3/4 x 9 3/4), 60 il., 37 tables, $31.75*

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PERCUTANEOUS ANGIOGRAPHY *by* **S. Swamy,** *Michael Reese Medical Center;* **Lewis Irwin Segal,** *Louis A. Weiss Memorial Hospital; and* **S. Mouli,** *Foster-McGaw Medical Center; all of Chicago, Illinois.* Numerous sketches explain the basic angiographic techniques and present solutions to common technical problems. Sections cover the roles of the patient, the doctor, and the equipment in angiography; specific angiographic methods; and patterns which have been classified by pathology rather than anatomy. *'77, 848 pp. (8 1/2 x 11), 1455 il., $80.00*

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INJECTION

Trandate Injection provides rapidly effective control of hypertensive emergencies

AS A BOLUS INJECTION...

"Labetalol given intravenously is highly effective for the acute reduction of blood pressure. In this series no serious side effects were encountered and the drug seems particularly suitable for use in hypertensive emergencies." (Rosei, E. A. et al, *Clin. Sci. mol. Med.*, 1976, **51**, 497s)

OR AS A CONTINUOUS INFUSION...

"Labetalol, given slowly by graded intravenous infusion, with continuous monitoring of arterial pressure, is our current treatment of choice in hypertensive emergencies." (Brown, J. J. et al, *Lancet*, 1977, **i**, 1147)

Subsequent treatment can be continued with the same drug given orally

"A practical advantage associated with labetalol is that oral treatment can be instituted immediately after using the intravenous form." (Rønne-Rasmussen, J. O. et al, *Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 805)

"There are many advantages to using a compound that can be given intravenously to control blood pressure in patients with small vessel disease or impaired renal function, which is then available for long-term oral therapy." (Joekes, A. M. & Thompson, F. D., *Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 789–793)

Trandate Tablets provide effective therapy in all grades of hypertension – including the difficult cases

"In this study (oral) labetalol reduced the blood pressure significantly in a group of patients with severe, drug-resistant hypertension." (Morgan, T. et al, *Med. J. Australia*, 1978, **i**, 393)

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Trandate

THE FIRST ALPHA-BETA-BLOCKER

RIGHT IN PRINCIPLE - WORKING IN PRACTICE

PRODUCT INFORMATION

PRESENTATION

Trandate Tablets 100mg, 200mg and 400mg each contain labetalol hydrochloride, 100mg, 200mg and 400mg, respectively. In packs of 50 and 250. PL 0045/0106, PL 0045/0107 and PL 0045/0109.

Trandate Injection: 20ml ampoules each containing 100mg (5mg/ml) labetalol hydrochloride. In boxes of 5 ampoules. PL 0045/0104.

INDICATIONS

Trandate Tablets are indicated for the oral treatment of all grades of hypertension, mild, moderate and severe.

Trandate Injection is indicated when rapid control of blood pressure is essential.

DOSAGE AND ADMINISTRATION

Trandate Tablets:

Adults: The initial dosage should not usually exceed 100mg 3 times daily. Adjustment of dosage should be gradual. Most cases are controlled with 600mg per day or less, but severe cases may require up to 2,400mg daily. Administration should be after a main meal.

Trandate Injection:

Adults: When rapid reduction of blood pressure is essential a dose of 50mg of Trandate should be given by intravenous injection over at least one minute. This may be repeated, if necessary, at 5-minute intervals but the total daily dose should not exceed 200mg. Alternatively it may be given by intravenous infusion. For this 2 ampoules of Trandate Injection are diluted to 200ml with sodium chloride and dextrose injection BP. This is infused at a rate of 2ml/minute until a satisfactory response is obtained when the infusion should be stopped. For most patients the effective dose is from 50 to 200mg but in phaeochromocytoma up to 300mg may be necessary.

Patients should be in the supine position when Trandate Injection is given and they should not stand or sit up within 3 hours of starting the administration. Once controlled, blood pressure reduction can be maintained with Trandate Tablets at a starting dose of 200mg 3 times daily.

Children: Not applicable.

For information on the use of Trandate with other drugs or for transfer to Trandate from other antihypertensive agents, see respective Data Sheets.

CONTRA-INDICATIONS, WARNINGS, ETC.

Trandate should not be given to patients with uncontrolled or digitalis-resistant heart failure, or with atrioventricular block. Caution is necessary in asthmatic patients or others prone to bronchospasm. Patients with severe liver damage will probably require lower doses of Trandate than usual. Unnecessary administration of drugs during the first trimester of pregnancy is undesirable.

Trandate Injection may cause excessive postural hypotension if patients are allowed to assume the upright position within 3 hours of administration.

Trandate Tablets may cause symptoms of postural hypotension if initial dosage is too high or increased too rapidly, but they are uncommon, except at very high doses, if used as recommended. Mild and usually transient side effects include: headache, tiredness, dizziness, depressed mood, lethargy, difficulty in micturition, epigastric pain and nausea and vomiting. Tingling in the scalp has occasionally occurred but is usually transient. Rarely, a lichenoid rash has been reported which disappears on drug withdrawal. Other skin rashes, blurring of vision, eye irritation and cramps have been reported but have been difficult to relate directly to Trandate treatment.

Warning: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the drug was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta-adrenoceptor blocking drug should be gradual.

A UNIQUE PROFILE IN HYPERTENSION

Full prescribing information is available on request.

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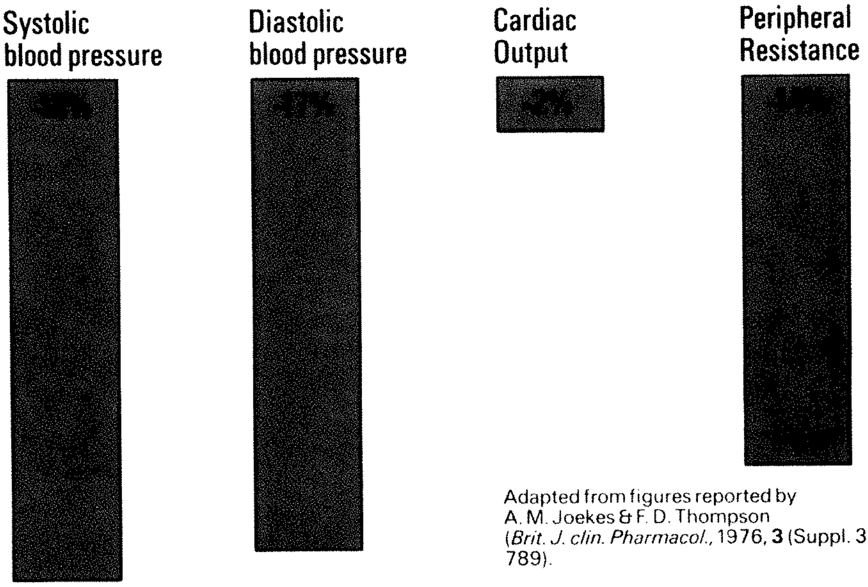
When blood pressure ha

Trandate

(labetalol hydrochloride)

has the right haemodynamic profile

HAEMODYNAMIC CHANGES FOLLOWING INTRAVENOUS TRANDATE



Adapted from figures reported by
A. M. Joekes & F. D. Thompson
(*Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 789).

The above figure shows the mean haemodynamic changes in 14 hypertensive patients given intravenous Trandate 0.5-1.0mg/kg

In essential hypertension the usual haemodynamic changes are increased blood pressure and peripheral resistance while cardiac output remains normal.

The authors of the above trial reported:
"Although there are striking changes in the blood pressure, this can be largely attributed to a fall in peripheral resistance with little change in pulse rate, stroke volume or cardiac output."

INTRAVENOUS TRANDATE
reduces blood pressure and peripheral resistance
without significantly affecting cardiac output

Colestid

colestipol

a non-systemic agent from Upjohn which lowers serum cholesterol

any authorities agree that elevated serum cholesterol an important factor in the development of heroslerosis. And, while it is not yet possible to sume that lowering cholesterol will reduce morbidity om coronary heart disease, most physicians accept e importance of maintaining serum cholesterol levels close to normal as possible.

olestid (colestipol), a new non-systemic agent veloped by Upjohn research, effectively lowers rum cholesterol by an average 12–15% in Type II perlipidaemic patients – those with elevated olesterol and normal or slightly elevated triglyc- ides![1,2,3] A lowering of serum cholesterol by 19% has een demonstrated with 10 grams of Colestid given ice a day.

olestid achieves a reduction in serum cholesterol by terfering with the normal enterohepatic circulation bile acids. Bile acids are synthesised in the liver from olesterol and are secreted in bile into the intestine. olestid works in the intestinal lumen, binding these le acids and increasing the rate of their excretion. ss bile acid is available for reabsorption from the estine, and the liver must convert additional olesterol to bile acid. The result is a reduction in asma cholesterol levels.

like other resin preparations, Colestid is well cepted by most patients. The odourless, tasteless anules may be mixed with a variety of liquids and ods, including fruit juices, milk, soups, pulpy fruits th a high water content, and carbonated beverages.

olestid has produced no known interference with the tion of coumarin anticoagulants, making it suitable for patients already under treatment for a heart condition. However, since Colestid may interfere with the absorption of certain drugs (e.g., chlorothiazide, tetracycline and penicillin G), the clinical response to concomitant medications should be closely monitored and appropriate adjustments made.

Most patients tolerate Colestid therapy very well. The most common side effect is mild constipation.

References: 1. Med. J. Aust. (1973). *1*:1223.
2. JAMA (1972). 222:676.
3. New Zealand J. Med. (1972). 76:12.

Prescribing Information

Presentations: Tasteless and odourless granules of colestipol hydrochloride. *Uses:* Adjunctive therapy to diet for treatment of hypercholesterolaemia, particularly Frederickson Type II. *Dosage and Administration:* Always mix with water or other fluids before ingesting. Oral total daily dosage for adult 15–30 grams. Take in divided doses 2–4 times daily. *Contraindications:* Hypersensitivity to colestipol. *Precautions, Warnings:* Not to be taken in dry form. Colestid may interfere with absorption of some drugs (e.g. penicillin G, tetracycline, chlorothiazide). Safety for use in pregnant women or children not established. *Package Quantities:* 30 x 5 g sachets; 250 g bottle. Each sachet or scoopful contains 5 g colestipol hydrochloride. *Further Information:* Colestid is not absorbed. It binds bile acids causing further cholesterol conversion to bile acids thus lowering serum cholesterol levels. *Basic NHS Costs:* 30 x 5 g sachets £8.90. 250 g bottle £13.76. Product Licence Nos. PL 0032/0055. PL 0032/0057. *Full Product information is available on request.*

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Calculate the Coronary risk

Prescribing Notes

Indications Treatment of hyperlipoproteinaemia, where full investigation has defined the abnormality, in conjunction with appropriate diet after diet alone has failed. Also indicated in: exudative diabetic retinopathy and in hyperlipoproteinaemia associated with diabetes; treatment of xanthomata associated with hyperlipoproteinaemia.

Dosage and administration 20-30mg/kg daily, divided into 2 or 3 doses after meals. If no adequate response after 6 months, consider additional measures or withdrawing drug.

Contraindications and warnings Due to increased gallstone frequency, do not use in patients with past or present gallbladder disease, or stones. On theoretical grounds, avoid 'Atromid'–S during pregnancy. Also avoid in impaired renal or hepatic function (e.g. biliary cirrhosis).
Caution is advised in patients with low serum albumin.
Patients also taking anticoagulants should have their anticoagulant dose halved and adjusted later as necessary.

Side effects: infrequent but include: transient increases in serum transaminase (these reflect adaptive responses of the liver); ventricular arrhythmia (one report); slight fluctuations in haemoglobin levels (isolated cases); reductions in white cells (occasional); one case of agranulocytosis (multiple drug therapy). Serial liver biopsy has confirmed the absense of 'Atromid'-S hepatoxicity in man.

Overdosage: administer symptomatic treatment.

'Atromid'-S is a trade mark for clofibrate
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helps reduce the coronary risk

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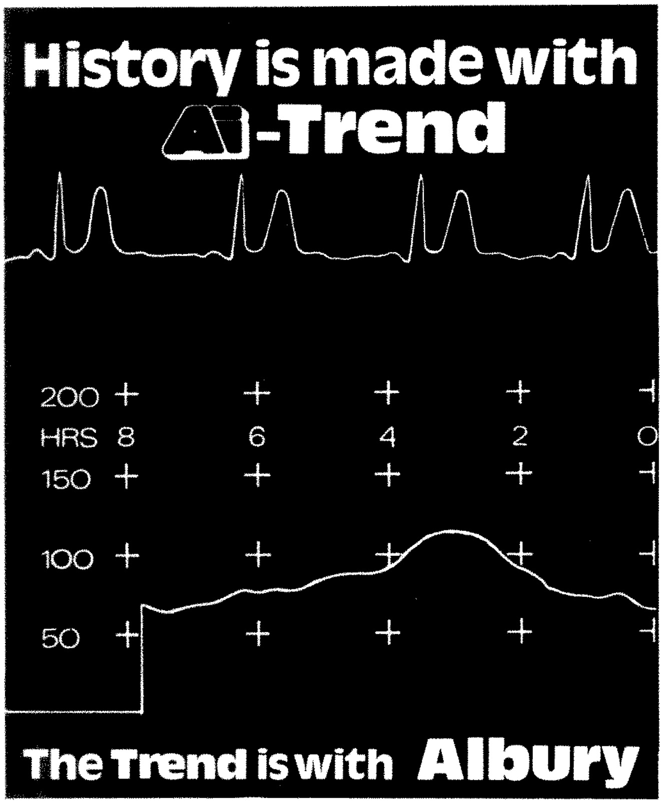
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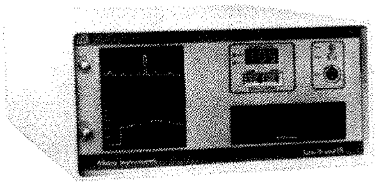

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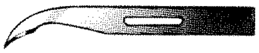

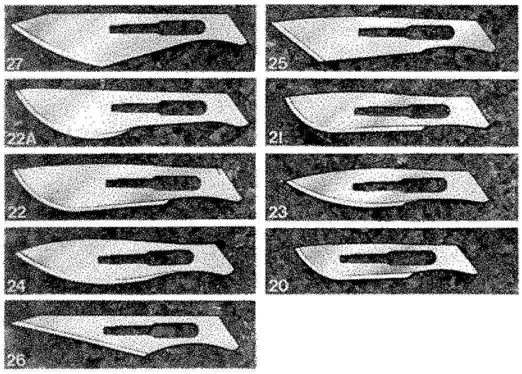

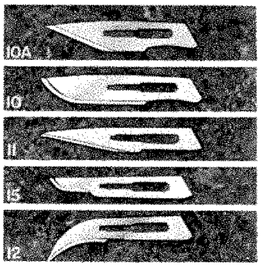

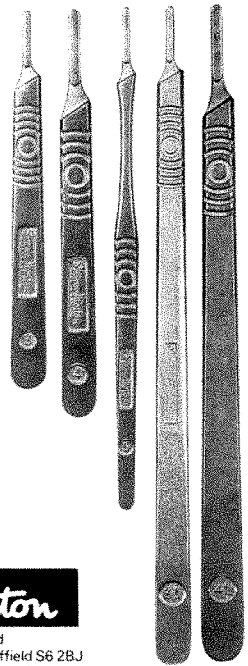

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These days, U.S. experts are taking care to recommend polyunsaturates.

1	Inter-Society Commission for Heart Disease Resources 1970. "Primary prevention of atherosclerotic diseases."	✓	4	American Medical Association Council on Foods and Nutrition 1972. "Diet and Coronary Heart Disease."	✓
2	American Health Foundation 1972. "Diet and Coronary Heart Disease."	✓	5	Select Committee on Nutrition and Human Needs 1977. "Dietary goals for the United States."	✓
3	White House Conference 1973. "Nutrition policies in the Seventies."	✓	6	American Heart Association Committee on Nutrition 1978. "Diet and Coronary Heart Disease."	✓

Six U.S. expert committees have now reported on diet and CHD.

All six recommend partial substitution of saturated fats by polyunsaturated fats.

The most recent report* advises that "the proportion of saturated fatty acids in the diet be brought into proper balance.

"To this end the levels of saturated fatty acids should be decreased to less than 10% of the total calories...

"Polyunsaturated fatty acids should supply up to 10% of the total calories, which can be accomplished easily."

Flora margarine is made with pure sunflower oil. It is higher in polyunsaturates than any other nationally available spread and the lowest in saturated fat.

**Flora-high in polyunsaturates.
The margarine that matters.**

*American Heart Association 1978. "Diet and coronary heart disease." General dietary recommendations - Section 2.

Corgard prescribing information

PRESENTATION

White, round, tablet engraved 'Squibb' and '241', scored on reverse, containing 80 mg nadolol.

Indications

For the long-term management of essential hypertension, either alone or in combination with other anti-hypertensive agents.

DOSAGE AND ADMINISTRATION

Initially 80 mg once daily. This dose may be increased by 80 mg increments at weekly intervals until an optimum response is obtained. Most patients respond to 240 mg or less, daily, but doses up to 640 mg have occasionally been used. In some patients it may be necessary to administer a diuretic, peripheral vasodilator and/or other anti-hypertensive agents in conjunction with nadolol in order to achieve satisfactory response. Dosage should be individually titrated.

Nadolol may be given in a once daily dosage without regard to meals.

Treatment of hypertension associated with phaeochromocytoma may require the addition of an alpha-blocking agent.

Contra-indications

Like other drugs in this class, nadolol is contra-indicated in bronchial asthma; allergic rhinitis during the pollen season; sinus bradycardia and 2nd and 3rd degree heart block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure; during and within 2 weeks of administration of adrenergic augmenting psychotropic drugs such as monoamine oxidase inhibitors.

Warnings

Exacerbation of angina and myocardial infarction have occurred after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with angina pectoris or other evidence of coronary artery insufficiency.

The normal precautions associated with the use of beta-adrenergic blockers should be followed.

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta-adrenergic blocker should be gradual.

Nadolol should be used with caution in patients with impaired renal or hepatic function.

The safety of nadolol in pregnancy has not yet been established, and it should only be given to nursing mothers if deemed essential.

Side-effects

These resemble those reported with other beta-blocking drugs and rarely require withdrawal of treatment. They include gastro-intestinal effects, bradycardia, fatigue, light-headedness, cold extremities, insomnia, paraesthesia and dryness of the mouth. Cardiac insufficiency, hypotension and AV block have occurred on rare occasions. Overdosage or exaggerated response should be treated supportively and symptomatically.

LEGAL CATEGORY

Prescription only.

Product Licence Number

0034/0186.

PACKAGE QUANTITIES

Bottles of 100 tablets.
Average daily cost of treatment 15p per day.

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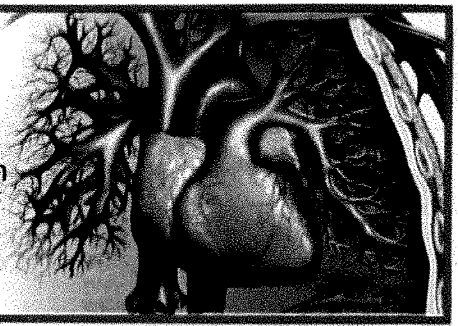

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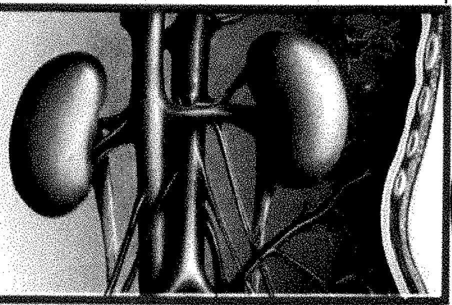

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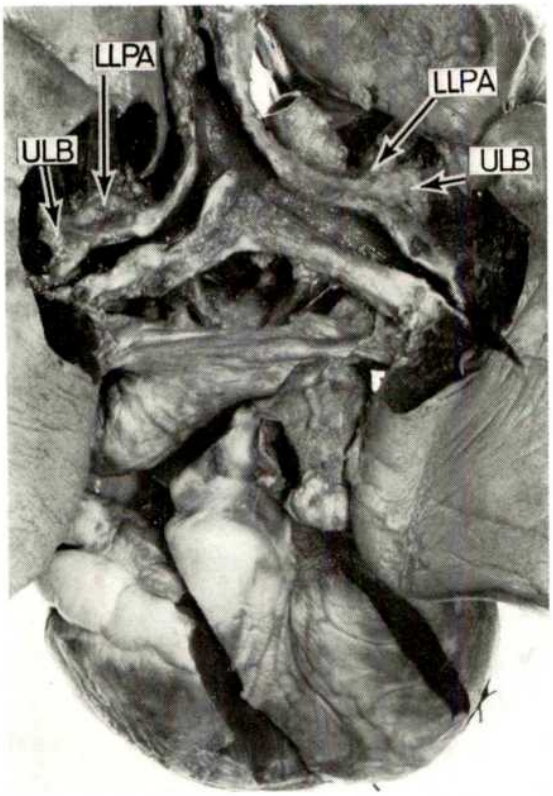


Fig. 6 *Posterior view of specimen with laevoisomerism dissected to show bilateral hyparterial (morphologically left) bronchi. Both lungs were bilobed and atrial appendages were of left morphology. The bronchi are hyparterial as both upper lobe bronchi (ULB) pass below lower lobe pulmonary arteries (LLPA).*

Associated lesions

Three patients had azygos continuation of the inferior vena cava. One patient had left juxtaposition of the atrial appendages (Fig. 8).

SITUS INVERSUS, DEXTROISOMERISM

In two patients atrial dextroisomerism was present, as suggested from the chest x-ray film and confirmed at necropsy in both. Both also had asplenia. In one the liver was central (visceral situs ambiguus) but in the other the liver was left sided (visceral situs inversus).

Atrioventricular junction (Fig. 9)

Two ventricles were present in one patient. The other had a univentricular heart of left ventricular type with outlet chamber of right ventricular type which was anterior and to the left of the main chamber.

Arterial junction

The patient with two ventricles had double outlet right ventricle with the aorta directly anterior, and the patient with a univentricular heart had single outlet (pulmonary atresia), the aorta arising from the outlet chamber.

Aortic arch

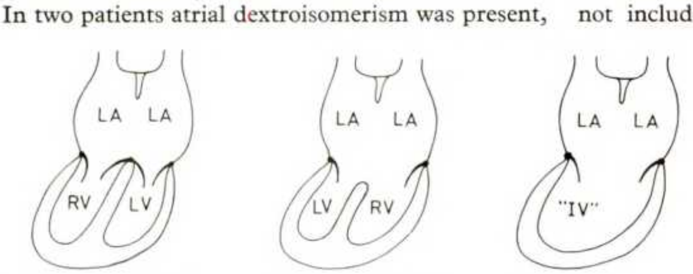
Both patients had a left-sided aortic arch.

Associated anomalies

Partial anomalous pulmonary venous return was found in one patient.

Discussion

Our study endorses the findings of others (Van Praagh *et al.*, 1964; Squarcia *et al.*, 1973) that a variety of chamber combinations can be found in hearts situated in the right chest with their long axis orientated to the right. We concur, therefore, with the opinion that the term dextrocardia conveys no information regarding chamber organisation and internal anatomy of the heart but should be used only for description of this cardiac position, a feature easily discernible from the plain chest radiograph. In this investigacion our cases not only had the greater part of the heart within the right hemithorax but also had the long axis and apex directed to the right. It is possible that cases were not included that others might have categorised



Ambiguus connections
1 case
RV to right and posterior of LV

Ambiguus connections
2 cases
RV to left and anterior of LV

Double inlet
1 case
Indeterminate type

Fig. 7 *Diagram illustrating atrioventricular connections in cases with situs ambiguus and laevoisomerism. Abbreviations as before. IV, univentricular heart of indeterminate type.*

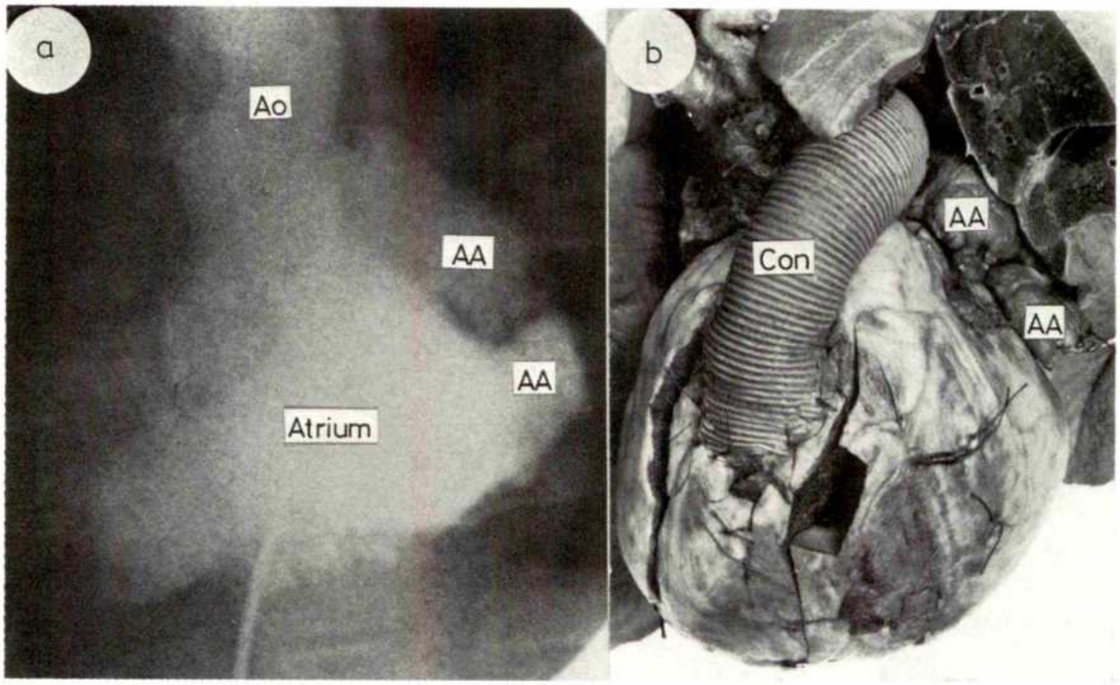


Fig. 8 (a) *Angiocardiogram from a patient with situs ambiguus with laevoisomerism showing left-sided juxtaposition of atrial appendages (AA) as demonstrated by atrial injection. Ao, aorta.* (b) *The necropsy specimen of this patient confirming presence of juxtaposed atrial appendages, both having left morphology. The patient had single outlet of heart with pulmonary atresia, and surgical correction with conduit (Con) was unsuccessful.*

as dextrocardia. However, as we have indicated, arguments concerning the precise definition of dextrocardia are unproductive, the important feature being the segmental arrangement in a heart. In this respect only two of our cases had 'normal' chamber arrangements, compared with 30 per cent of those analysed by Van Praagh *et al.* (1964), though only 7 per cent of those studied by Lev *et al.* (1968) had normal chamber connections. It is possible that these differences reflect the mode of selection of cases. Thus, as shown by the earlier investigations, it is essential to utilise a segmental approach in order adequately to diagnose and classify the cases. We have not, however, found previous approaches (Van Praagh *et al.*, 1964; Squarcia *et al.*, 1973; Van Praagh and Vlad, 1978) to be universally applicable to the anomalies encountered. In contrast, utilisation of the system advocated by Tynan *et al.* (1979) has enabled all hearts to be described simply and unambiguously.

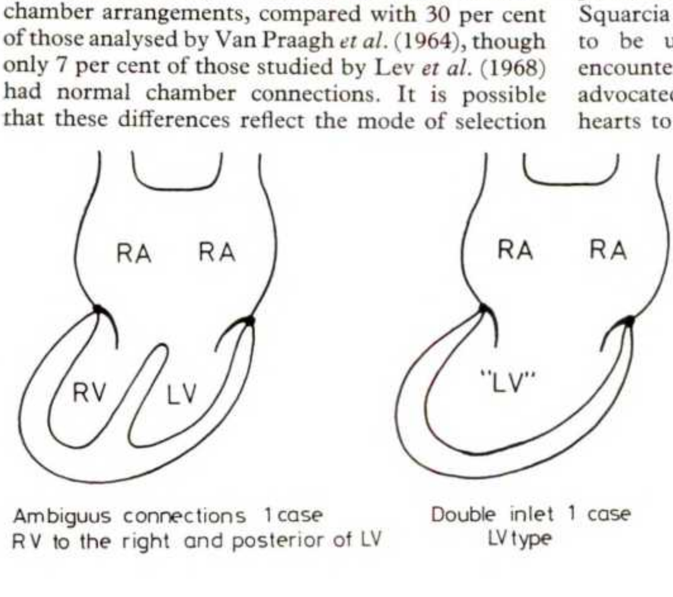

RA
RA
RV
LV
Ambiguus connections 1 case
RV to the right and posterior of LV
RA
RA
"LV"
Double inlet 1 case
LV type

Fig. 9 *Diagram illustrating the atrioventricular connections found in two patients with situs ambiguus and dextroisomerism.*

The hearts investigated here highlight the deficiencies in diagnostic approaches which do not distinguish clearly between anatomical connections and spatial relations.

In the hearts we examined, atrial situs was determined from bronchial anatomy on plain chest radiography. In this way not only could situs solitus and inversus be identified but the laevoisomeric and dextroisomeric forms of situs ambiguus could be distinguished. Atrial situs was confirmed in the cases coming to necropsy. We believe this method of categorising situs to be preferable to those relating atrial morphology to the state of the spleen. Furthermore, if there is doubt from the plain film, bronchial morphology can easily be confirmed by tomography (Partridge *et al.*, 1975) and there is better correlation between atrial and bronchial anatomy than between atrial morphology and presence or absence of splenic tissue or multiple spleens (Macartney *et al.*, 1978).

When describing the ventricular segment of the heart, we found it necessary to be able to describe connections of the atria to the ventricles independently both of spatial relations of chambers within the ventricular mass and of the morphology of the ventricular chambers. Thus, in our cases we found all five types of atrioventricular connection considered possible by Tynan *et al.* (1979), namely concordant, discordant, ambiguus, double inlet, and absence of one atrioventricular connection. In the last category absent right but not absent left atrioventricular connection was seen. The provision of the category for ambiguus connection was necessary to describe the connections in the hearts with situs ambiguus and two ventricles, as the terms concordance and discordance are inappropriate for this arrangement (Tynan *et al.*, 1979). Our cases also illustrated the usefulness of describing type of connection separately from mode of connection, since the ambiguus connection was effected through a common valve in five cases, but through separate right and left valves in one case.

These cases also serve to illustrate what we believe to be a further refinement (Shinebourne *et al.*, 1978) of our initial approach to this connection (Shinebourne *et al.*, 1976). Following Van Praagh's lead, we initially described ventricular relations with ambiguus connection in terms of the loop, as was recently commented upon by Freedom *et al.* (1978). However, because of the additional connotations of 'd- and l-loop', we now prefer to describe the ventricular relations simply in terms of right/left and antero/posterior orientation. One reason for this is the possibility of a 'criss-cross' heart (Anderson *et al.*, 1974) with an ambiguus connection. Previously in a criss-cross heart, we had used 'd-loop' to describe the relation where the morphologically right ventricle was right sided. However, if a criss-cross situation were found with an ambiguus connection, would the relation be described as 'd-loop' or 'l-loop'? As Freedom *et al.* (1978) indicate, the current concept of the loop (Van Praagh and Vlad, 1978) makes it independent of situs. As such, in situs ambiguus it is simply being used to describe ventricular relations. Thus, in the criss-cross situation the left-sided right ventricle, having achieved its position as a consequence of cardiac rotation, can still be recognised as belonging to a d-loop. Is it not, however, simpler to describe the ventricular position in terms of right/left and antero/posterior position rather than asking the observer to interpret the presumed embryological looping of the heart tube? We also submit that simple usage of the right/left and antero/posterior co-ordinates is more useful and more accurate than the terms 'inversion' and 'non-inversion'. The 'inverted' ventricles of classical corrected transposition in situs solitus are rarely, if ever, the mirror image of the normal ventricular arrangement: in the presence of atrioventricular discordance the ventricles tend to be more side by side with horizontal inclination. Furthermore, there is no consensus as to what 'ventricular inversion' describes. For some authors, 'ventricular inversion' in situs inversus describes ventricles occupying the *normal* position for the solitus individual with a normal heart, with the right ventricle anterior and to the right (Espina-Vela, 1978). Such different interpretations are avoided by the use of simple adjectives such as right, left, anterior, and posterior.

The value of describing ventricular morphology independently of the connection is well illustrated by our cases with absence of the right atrioventricular connection ('tricuspid atresia'). These hearts illustrate the wide variability found in hearts having the atrial morphology of classical tricuspid atresia, a possibility predicted in our previous studies (Anderson *et al.*, 1977). Thus, univentricular hearts of right ventricular type, left ventricular type, and indeterminate type were found with absent right atrioventricular connection. We find it difficult to describe these hearts using the loop concept. The finding of such variability in ventricular morphology in hearts with 'tricuspid atresia' has considerable surgical significance. Rudimentary chambers may be posterior or anterior, right sided or left sided, or absent. Most posterior chambers are not suitable for incorporation into the circulation in 'corrective' procedures. We also do not know the effect that ventricular morphology will have on the possible outcome of a Fontan procedure, and clearly this is another factor which must be considered when assessing these cases for possible operation (Fontan *et al.*, 1978).

It is of note that several hearts in our series had the morphology of a main chamber of right ventricular type with a rudimentary chamber of left ventricular type. Five cases were identified (16·5%), three with double inlet connection, and two with absence of the right atrioventricular connection. We believe that in part this relatively high prevalence is the result of an awareness of the anomaly, since we are now finding this malformation with increasing frequency in hearts both with and without dextrocardia (Keeton *et al.*, 1979). Again, identification of this type of ventricular morphology in the univentricular heart is important since it affords a good guide to the likely disposition of the conducting system (Anderson *et al.*, 1978).

Juxtaposition of the atrial appendages was not infrequent in our series. Otero Coto *et al.* (1978) have also pointed to an association between right-sided apex and juxtaposition with a left-sided aorta. However, the aorta was left sided in only one of our cases. All the cases were identified during life, a possibility discussed by Deutsch *et al.* (1974).

At the arterial junction we again found categorisation to be facilitated by describing separately the connections, the arterial relations, and infundibular morphology. It seems to us that if this is done there can be little room for controversy concerning such matters as 'transposition' or the 'conus'.

In conclusion, we have studied a series of patients whose hearts were within the right hemithorax with their long axes orientated to the right, this being the only information to be drawn from the term 'dextrocardia'. The identification and categorisation of the extremely varied chamber arrangement within these hearts was greatly facilitated by use of a descriptive system accounting separately for connections, relations, and morphology.

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Venous circulation of the human cardiac conduction system

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SUMMARY The venous bed of the sinuatrial node in 25 human hearts and the atrioventricular conduction system in 50 human hearts were investigated after injection into different veins of the heart. Blood is drained from the sinuatrial node in two directions; that from the intermediate and upper parts of the node blood is directed upwards, draining into the junctional area of the superior vena cava with the right atrium. From the intermediate and the lower parts of the node the venous return is directed downwards, draining directly into the right atrium between the musculi pectinati.

The venous return from the ventricular conduction system is drained by three routes. The main route from the atrioventricular node and the atrioventricular bundle passes into the thebesian vein, which opened in 78 per cent of the cases studied into the right atrium next to the coronary sinus. The other route from the node and bundle is via a vein which accompanies the atrioventricular nodal artery, draining eventually into the middle cardiac vein. The third route takes venous blood from the lower part of the atrioventricular bundle and is drained to the tributaries of the great cardiac vein, interconnecting with the branches of the above two veins. The venous return from the ventricular bundle-branches is drained into the oblique septal veins.

The venous drainage of the conduction system was described by Geraudel (1928), Ábrahám (1964), and Kennel and Titus (1972), all of whom thought that blood was drained from the atrioventricular node by thebesian veins into the right ventricle. Truex and Schwartz (1951) also described the veins of the atrioventricular conduction system, but they regarded them as dilated sinusoids and maintained that they played an important role in facilitating the influence of toxins upon the conduction system.

In the present paper an attempt will be made to supplement and enlarge the data concerning the localisation of venous drainage of different segments of the conduction system and their interconnections.

Subjects and methods

The venous drainage of the sinuatrial node has been visualised in 25 human hearts (13 men, 12 women) by injecting the thebesian veins opening into the superior vena cava in the region of the node and opening between the musculi pectinati of the right atrium. The veins draining the region of the atrioventricular node and atrioventricular bundle have been visualised in 50 hearts (27 men, 23 women) by injecting various veins, namely those opening into the upper part of the great cardiac vein, those opening into the upper part of middle cardiac vein, and, finally, by injecting thebesian veins opening into the right atrium. The substances used for injection included a solution of Indian ink in 2 per cent gelatin, a pigment Seabondorange suspension in 2 per cent gelatin, and a radiopaque substance, Mikropaque.

The regions of the sinuatrial nodes obtained from 16 hearts and those of the antrioventricular nodes and atrioventricular bundles obtained from 25 hearts were processed for histological examination by serial sectioning. The sinuatrial nodes were cut transversely and longitudinally; the atrioventricular nodes and bundles were sectioned transversely. The sections were stained with a trichrome stain utilising a blue counterstain, haematoxylin and eosin, and Weigert's iron haematoxylin.

The rest of the hearts were evaluated by dissection under a dissecting microscope after hydydration and clearing in methylsalicylate or in glycerin. Those injected with Micropaque were evaluated with the aid of *x*-ray films.

All the hearts were obtained from the Faculty Department of Forensic Medicine. The age range was 10 to 70 years. None of the patients from whom the hearts were obtained was reported to have had a history of heart disease.

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Observations

SINUATRIAL NODE

The sinuatrial node is drained (Fig. 1) by one to three small veins, 150 to 500 μm in diameter which perforate the wall of the superior vena cava and open at its anterior circumference just above the junction of the vein with the right atrium. The openings are irregularly distributed along the whole anterosuperior circumference of the superior vena cava. The draining veins originate from the plexiform network of postcapillary venules, 10 to 30 μm in diameter, which fuse to form venules 50 to 150 μm thick. The injected specimens show (Fig. 2) that such veins collect together from the upper and the intermediate parts of the sinuatrial node to anastomose with similar veins draining its lower part, opening by two to three openings between the trabeculae in the crest of the auricular appendage. The two draining systems are extensively interconnected and no distinct borderline separating one from the other could be recognised.

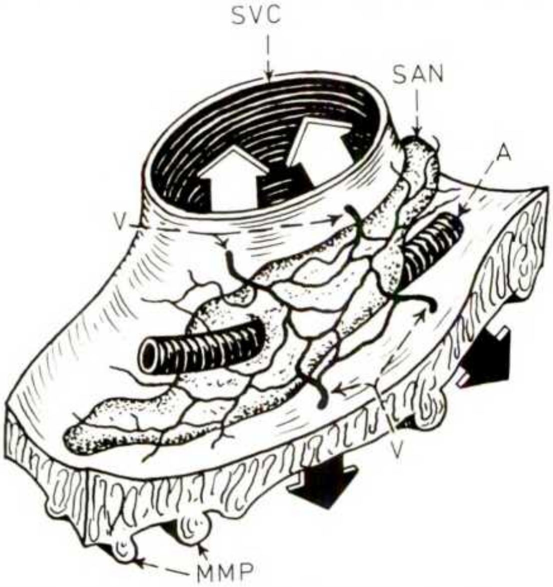

Fig. 1 *Venous drainage of the sinuatrial node: the upper and the intermediate part of the node (SAN) drains into the superior vena cava (SVC—white arrows), the intermediate and the lower part of the node drains into the atrial appendage, the openings being placed between the musculi pectinati (MMP—black arrows). A, sinuatrial node artery; V, veins draining the sinuatrial node.*

The preparations disclose that most of the larger venules draining blood from the sinuatrial node pass parallel to the long axis of the node (Fig. 2).

Adequately injected specimens reveal that the ratio of postcapillary veins to fibres of the conduction system is 1:1 or 1:2. The initial segments of postcapillary veins passing between the fibres of the conduction system have their walls closely attached to those fibres (Fig. 3). We did not find any vein which, by virtue of either its size or position, could have been considered as a venous channel accompanying the large central artery of the sinuatrial node. Only small venules were found in the vicinity of the adventitia of that artery. Larger veins were found only beyond the boundaries of the node (Fig. 4).

ATRIOVENTRICULAR NODE, ATRIOVENTRICULAR BUNDLE, AND VENTRICULAR BUNDLE-BRANCHES

The injection methods enabled us to visualise several venous pathways draining the atrioventricular node (Fig. 5). The main draining vein is a thebesian vein, 0·5 to 2 mm thick, buried in the

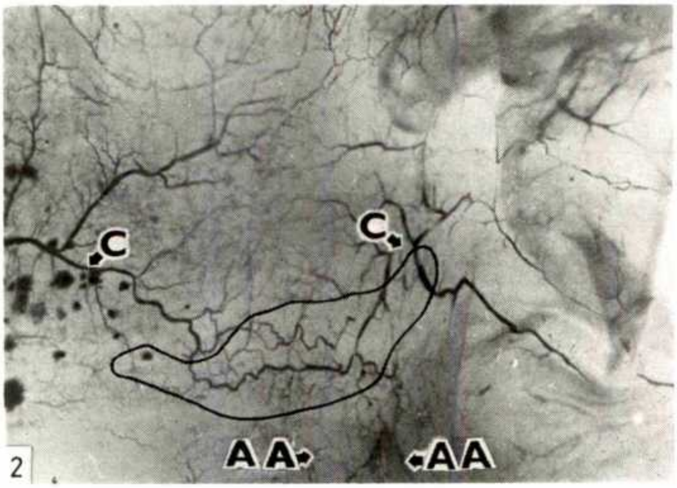

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Fig. 2 *The network of injected veins (Mikropaque) draining the SA node into the superior vena cava (C) and the right atrial appendage (AA). Cleared in methylsalicylate. Man aged 37 years. Plotted in the figure is the projection of the SA node.*

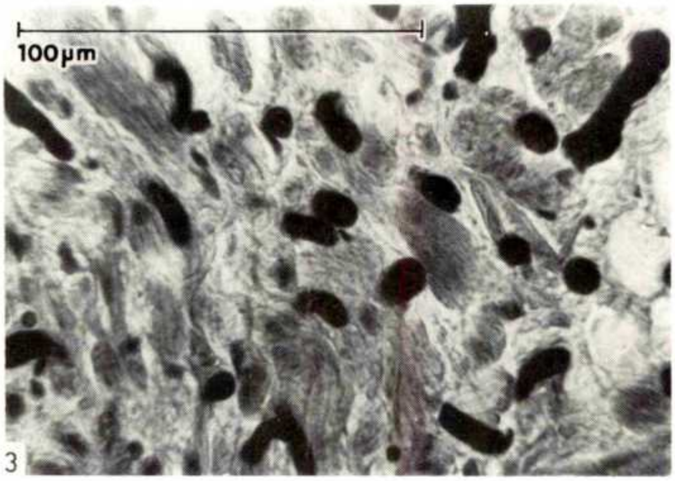

Fig. 3 *The capillary segment of venules passing either transversely or obliquely between the fibres of the sinuatrial node. Blue trichrome stain, injection with gelatine-solved Indian ink. Man aged 38 years.*

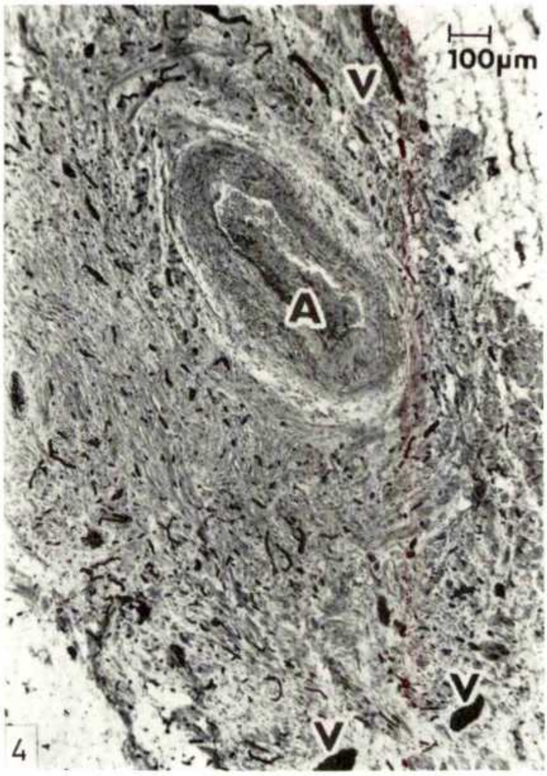

Fig. 4 *Transverse section through the SA node. The vessels have been injected with gelatin-solved Indian ink. Most of the vessels appear to be cross-sectioned or on oblique section. In the upper and lower part of the node are wide draining veins (V). A, the artery of the SA node. Haematoxylin and eosin. Man aged 38 years.*

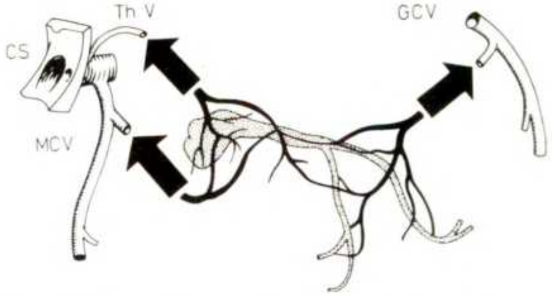

Fig. 5 *Venous drainage of the ventricular conduction system. The black arrows indicate the venous drainage from the atrioventricular (AV) node, the AV bundle, and the branches into the veins of the great cardiac vein (GCV), into the middle cardiac vein (MCV), and into the right atrium in the vicinity of coronary sinus (CS) through a thebesian vein (Th V).*

septum which opens into the right atrium in the vicinity of the coronary sinus. The vein collects blood from the upper part of the interventricular septum, the membranous septum, and the lower part of the interatrial septum. In 39 cases it was found to communicate by one or two openings with the right atrium, entering the atrium up to a distance of 1 cm anteriorly or posteriorly to the ostium of the coronary sinus. In eight instances it opened into the coronary sinus and in three into the middle cardiac vein. The trunk of the vein, 0·5 to 1 cm long, can be seen under the endocardium and its tributaries, three to seven in number and 50 to 300 µm thick, pass along on the surface of the node, occasionally extending into the substance of the node. They are parallel to its long axis, but occasionally they are diagonal so that the transverse sections through the node may show their transverse or oblique sections (Fig. 6). The above

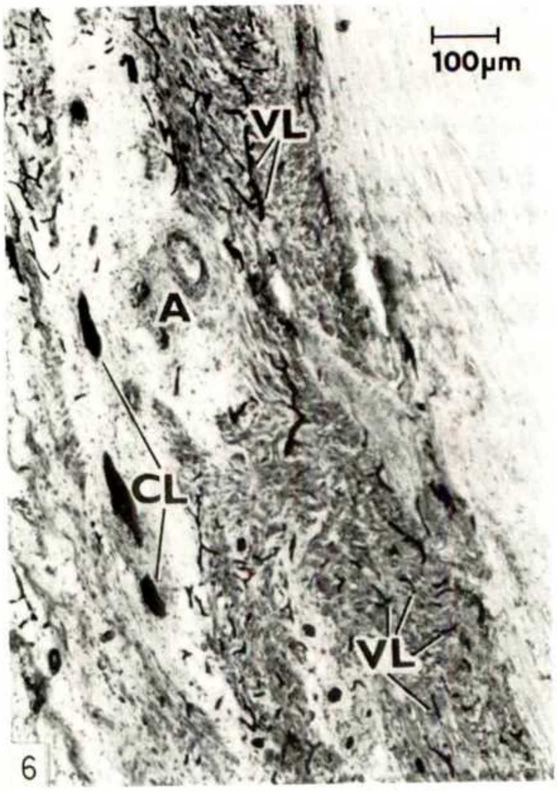

Fig. 6 *The veins of an AV node (gelatin-solved Indian ink). The node shows networks of small venules (VL). There are larger collecting venules (CL) at the margin of the node. A, artery of the AV node. Blue trichrome stain. Man aged 64 years.*

branches receive small venules and venous postcapillaries, 10 to 30 μm thick, which interweave with the fibres of the atrioventricular node itself. The ratio appears to be one postcapillary venule to one to three conduction fibres. The other pathway of venous drainage from the node is a vein, 0·4 to 1 mm thick, which collects blood from the posterior and the intermediate part of the node and the adjacent areas of the septum. The vein passes along through the atrioventricular sulcus made up of loose connective tissue beneath the coronary sinus and opens into the middle cardiac vein (Fig. 5) at its junction with the coronary sinus. If the small cardiac vein is well developed, the vein may open into it. The vein passes along with the artery of the atrioventricular node, or may take a separate course several millimetres distant from this artery. The two draining veins have an extensive communicating anastomotic network. The branches of the septal vein draining blood from the atrioventricular node not only pass through the node but they proceed further, running through the atrioventricular bundle to communicate with the veins of the right and left bundle-branches. The majority of vessels, 15 to 30 μm thick, are parallel to the fibres of the conduction system (Fig. 7 and 8). In the lower part of the atrioventricular bundle they show smooth transitions into the septal veins which drain anteriorly into the upper part of the great cardiac vein and posteriorly into the middle cardiac vein. The injection from the septal thebesian vein is capable of filling the veins opening into the great cardiac vein. Similarly, an injection into the great cardiac vein will fill the main branches of the septal thebesian vein. The postcapillary venules of the right and left bundle-branches run parallel with the fibres of the bundle-branches themselves (Fig. 9 and 10). The upper part of the bundle-branches is drained by both veins of wide calibre (50 to 80 μm) and of narrow calibre, whereas the lower part is drained only by narrow veins (10 to 20 μm). A more satisfactory injection of the venules was achieved in areas of the conduction system remote from the septal endocardium. The veins of the bundle-

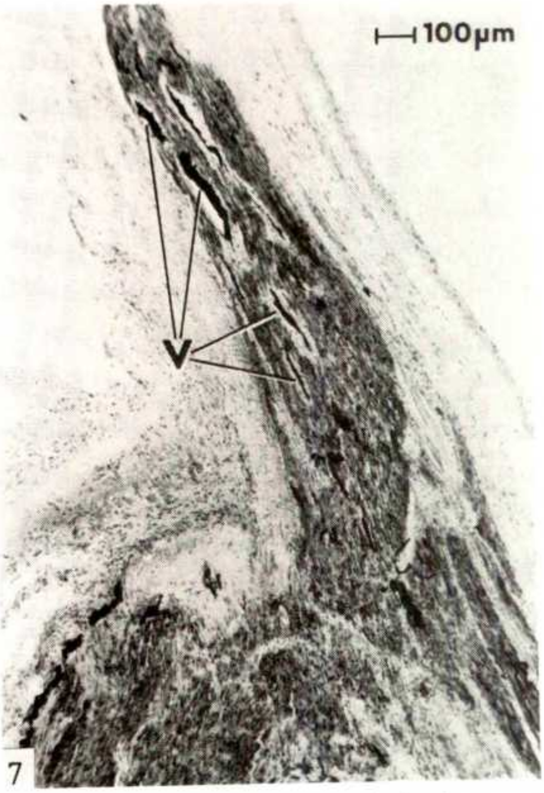

Fig. 7 *Veins (V) of the atrioventricular bundle injected with gelatine-solved Indian ink. They pass longitudinally along with the fibres of the conduction system. Haematoxylin and eosin. Woman aged 56 years.*

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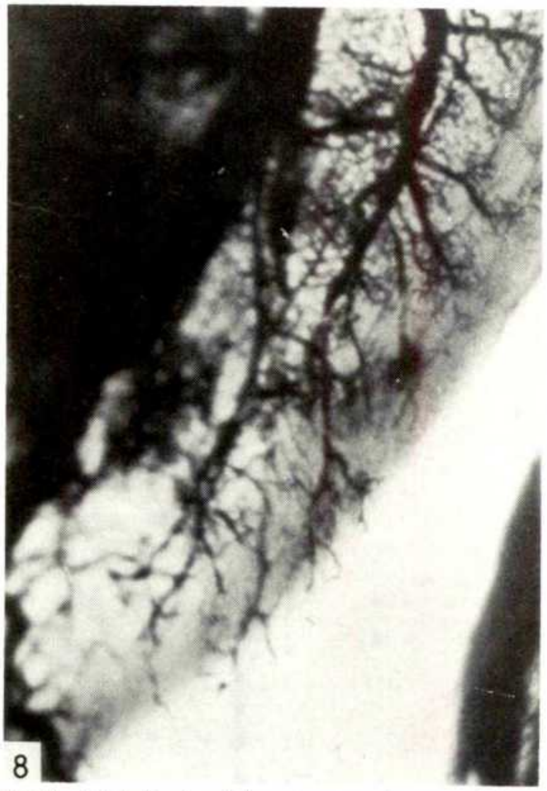

Fig. 8 *Injected veins of the upper posterior part of the membranous septum at the site of the atrioventricular bundle, cleared in glycerin before histological processing. Compare with Fig. 7. Woman aged 56 years.*

branches were seen to open into the oblique septal veins, which in turn communicated anteriorly with the great cardiac vein and posteriorly with the middle cardiac vein. Since the vascular bed of the great and middle cardiac veins and the thebesian system of the chambers are extensively interconnected, there are many possibilities for venous drainage of the ventricular bundle-branches (Elišková and Eliška, 1969).

Discussion

The injection of the sinuatrial node allows us to recognise that its venous system drains into the superior vena cava above the node and into the upper part of the atrial appendage below the node. The two systems are extensively interconnected since the Indian ink injected into the opernings of the veins of one group appears in the openings of the other group of veins. Such an anatomical pattern rules out the possibility of venous congestion in the region of the node itself. The upper group of draining veins resembles by its course that of vasa vasorum. In contrast, the lower group of vessels resembles by its course and openings typical thebesian vessels. When adequately injected, the specimens did not show any differences in the density of venous drainage of the conduction system of the sinuatrial node and that of normal myocardium bordering on the node.

Similarly, the veins of the atrioventricular node, the atrioventricular bundle, and its branches also form an extensive anastomotic network. Such a pattern will facilitate venous drainage directly into the right chamber, and into the middle cardiac vein and great cardiac vein. Here again, the venous drainage can be considered nigh on perfect.

Truex and Schwartz (1951), using reconstruction studies, showed that the veins of the atrioventricular bundle formed a sinusoid system most frequently opening into the coronary sinus and into the atrium. These authors thought that toxins in infectious

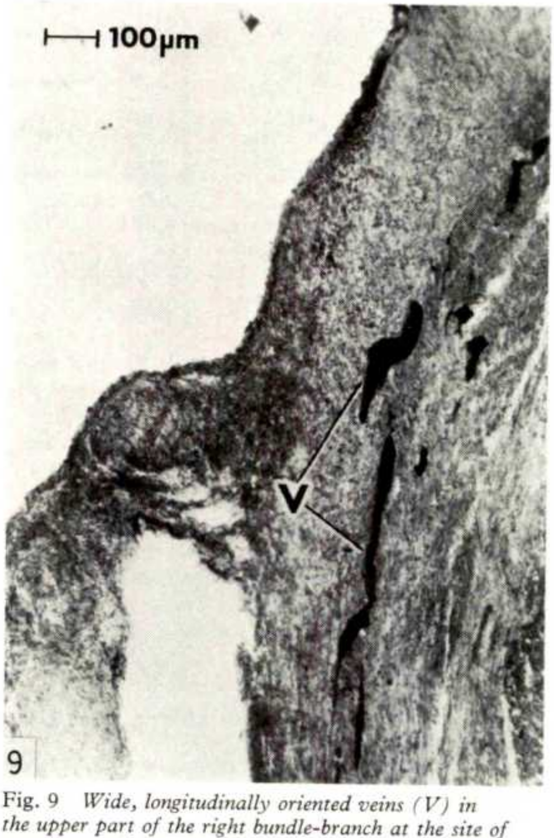

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Fig. 9 *Wide, longitudinally oriented veins (V) in the upper part of the right bundle-branch at the site of attachment of the septal leaflet of the triscupid valve. Blue trichrome stain. Man aged 30 years, injection with gelatine-solved Indian ink.*

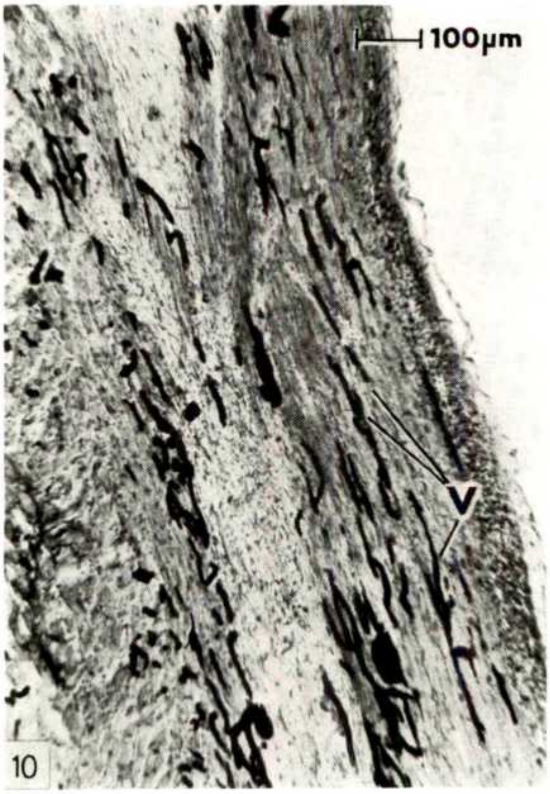

Fig. 10 *Longitudinally orientated veins (V) of the left bundle-branch, 1 cm beyond its origin from the branching bundle. Blue trichrome stain. Man aged 30 years, injection with gelatine-solved Indian ink.*

diseases and metabolites in myocardial infarction were capable of influencing the conduction system. Recently, similar conclusions were reached by Davies (1971).

Our preparations allowed us to conclude that the venous drainage of the conduction system was composed of regular postcapillary veins and venules which assumed the appearance of irregular sinusoids in their terminal segments, whence they passed through the atrioventricular node. The course of the larger veins is predominantly longitudinal, parallel with the long axis of the node and the atrioventricular bundle. The cross-sectioned or obliquely sectioned veins seen in histological preparations usually represent tributaries of these longitudinal veins. Lympho-venous anastomoses, such as found in our previous studies (Eliška and Elišková, 1975, 1976), were not encountered in the injected hearts used for the present study.

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Left ventricular function in rheumatic mitral stenosis
Clinical echocardiographic study

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SUMMARY Echocardiography was used to examine the extent and significance of impairment in left ventricular function in 20 patients with rheumatic mitral stenosis. Indices of left ventricular performance —normalised mean rate of circumferential fibre shortening (Vcf), ejection fraction, normalised posterior wall velocity, and stroke volume were reduced. The impairment in left ventricular function was related to the degree of functional disability (NYHA), right ventricular dilatation, and left atrial enlargement. Vcf was inversely related to both the internal right ventricular diameter ($r = -0{\cdot}767$, $P < 0{\cdot}001$) and the degree of left atrial enlargement ($r = -0{\cdot}554$; $P < 0{\cdot}05$). The normalised velocity of the interventricular septum and the maximum systolic and diastolic endocardial velocities were also reduced.

These results suggest that abnormalities in contractility of left ventricular myocardium are responsible for the impaired myocardial function in patients with mitral stenosis and that such impairment is clinically significant.

Rheumatic mitral stenosis is one of the commonest valvular heart lesions in Egypt and other developing countries. The only effective treatment is surgical. However, the results of operation, morbidity, and mortality are governed not only by the mechanical defect but also by the state of the myocardium. The presence of such a myocardial factor in rheumatic mitral stenosis (Harvey *et al.,* 1955; Fleming and Wood, 1959) has remained speculative until recently (Feigenbaum *et al.,* 1966; Curry *et al.,* 1970; Heller and Carleton, 1970; Holzer *et al.,* 1973). Since rheumatic heart affection is more severe and the degree of valvular damage is greater in developing countries than in industrialised Western communities (El-Sherif, 1975), it seems appropriate to examine the incidence and extent of left ventricular dysfunction in Egyptian patients. Left ventricular dimensions and function were therefore investigated in a group of patients with rheumatic mitral stenosis who were referred for mitral commissurotomy. In addition, the clinical correlates and the changes in right ventricular and left atrial dimensions were examined. Echocardiography had been used in this study for measurements of cardiac chamber dimensions and for the assessment of left ventricular performance. Good correlation between angiocardiographic and echocardiographic measurements of left ventricular dimensions has already been shown (Pombo *et al.,* 1971; Feigenbaum *et al.,* 1972).

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Methods

Twenty patients with isolated rheumatic mitral stenosis were investigated. All patients were evaluated clinically and mitral commissurotomy was found necessary. Symptoms, that is degree of dyspnoea and effort intolerance, were classified according to New York Heart Association (NYHA). Patients with hypertension (systolic blood pressure > 170 mmHg or diastolic > 100 mmHg), ischaemic heart disease, or other possible causes for left ventricular enlargement or impairment were excluded. The severity of mitral stenosis was determined from history, physical examination, chest radiograph to assess the size of the left atrium and pulmonary venous congestion, and the electrocardiogram to detect right ventricular hypertrophy and left atrial enlargement. The E-F slope of the mitral valve in the echocardiogram was also determined to assess the severity of mitral stenosis.

ECHOCARDIOGRAPHY

Recording technique

The echocardiograms were recorded with a Unirad ultrasonoscope model 849 Sono III-GZD using a 2·25 MHz transducer with an active diameter of

13 mm and internal focus 4 to 7 cm, with a repetition rate of 10·0 impulses/s. The ultrasonoscope was coupled to a strip chart recorder. Recordings were obtained at a paper speed of 50 mm/s and when necessary 100 mm/s. Each patient had an electrocardiogram recorded simultaneously with the echocardiogram. All patients were examined in the supine position. The transducer was placed on the third, fourth, or fifth intercostal space, just to the left of the sternum, and the ultrasonic beam was directed posteriorly and slightly medially until the echogram of the anterior leaflet of the mitral valve was identified. The transducer was then rotated inferolaterally until the echoes from the endocardial surface of the interventricular septum and the posterior left ventricular wall were clearly visualised. Measurements of left ventricular dimensions were made at an angle in which fragmented echoes of the mitral valve together with the interventricular septal and posterior wall endocardial echoes could be recorded (Fig. 1). Particular care was taken to standardise the pathway of the ultrasonic beam through the left ventricle, to identify correctly the internal and external surfaces of the left ventricular walls. The transducer was then directed in a posterior cephalad and medial manner to record the aorta and left atrium. The transducer was then rocked inferolaterally to the point at which the aortic valve cusps could be visualised. Echocardiographic measurements were made only on recordings of good quality.

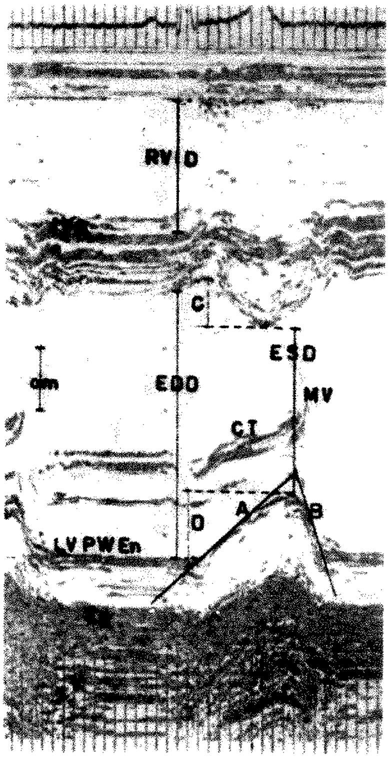

Fig. 1 *Echocardiographic measurements. The transducer was directed towards the cavity of the left ventricle immediately below the mitral valve leaflets. Fragmentary echoes of the mitral valve (MV) are seen. EDD, end-diastolic diameter of left ventricle; ESD, end-systolic diameter of left ventricle; IVS, interventricular septum; LVPW, left ventricular posterior wall. The slope of the tangent to the steepest part of the endocardium of the left ventricular posterior wall was measured in systole (A) and diastole (B) to determine the maximal systolic endocardial velocity and the maximal diastolic endocardial velocity. (C) Interventricular septal excursion. (D) Posterior wall excursion. RVID, right ventricular internal diameter; En, endocardium; Ep, epicardium; CT, chordae tendineae; RV, right ventricle.*

Measurements and calculations

The left ventricular echocardiographic dimensions were measured from the endocardial echo of the posterior wall to the endocardial echo of the left side of the interventricular septum. Measurements at end-diastole (EDD) were made at the peak of the R wave of the QRS, and measurements at end-systole (ESD) were made at the point of the smallest distance separating the septum from the posterior wall (Fig. 1). The left ventricular ejection time (LVET) was measured from the aortic valve echogram or from a simultaneously recorded carotid pulse. Septal (IVST), posterior left ventricular thickness (LVT), and right ventricular internal diameter (RVD) were measured at the peak of the R of the QRS (Fig. 1). Posterior left ventricular wall excursion (PWE) was measured from the most posterior point of the left ventricular endocardial tracing to the most anterior point in systole (Fig. 1). Similar points at the beginning and peak of the septal systolic excursion were selected to measure septal excursion (IVSE). The maximal systolic endocardial velocity (MSEV) was measured from the slope of the tangent to the steepest part of the endocardium of the left ventricular posterior wall in systole as previously described (Kovick *et al.*, 1975) (Fig. 1). The maximal diastolic endocardial velocity (MDEV) was measured similarly in diastole.

Other measurements made from the echocardiogram were the left atrial (LAD) and aortic root (AoRD) dimensions at end-systole (Brown *et al.*, 1974) (Fig. 2). Mitral valve diastolic excursion was measured as the vertical line from the lowest point of the mitral echogram (C) to the E point. The mitral diastolic closure slope (E-F) was measured.

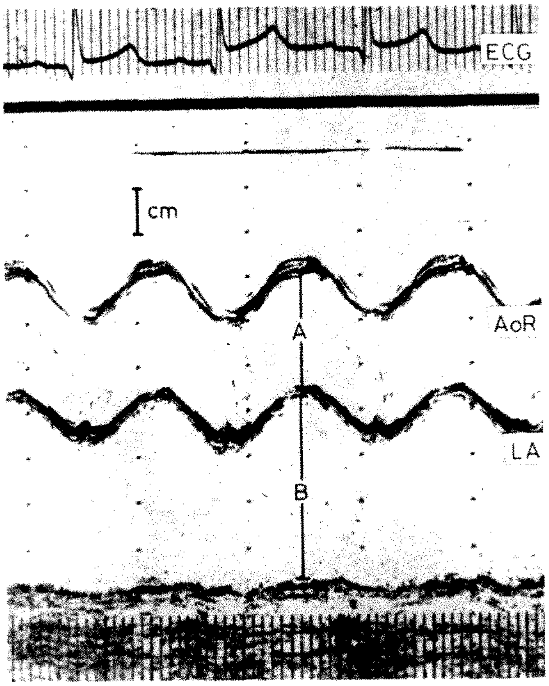

Fig. 2 *Echocardiographic measurements. The transducer was directed towards the aortic root (AoR). A, aortic root diameter; B, left atrial diameter; LA, left atrial cavity.*

Left ventricular volumes were derived by cubing EDD and ESD. The difference between end-diastolic volume (EDV) and end-systolic volume (ESV) was the left ventricular stroke volume (SV). These volumes were also used to calculate the ejection fraction (EF):

$$\mathrm{EF} = \frac{\mathrm{EDV} - \mathrm{ESV}}{\mathrm{EDV}}$$

The normalised mean rate of circumferential fibre shortening (Vcf) was calculated as:

$$\mathrm{Vcf\ (circ/s)} = \frac{\mathrm{EDD} - \mathrm{ESD}}{\mathrm{LVET} \times \mathrm{EDD}}$$

The normalised mean posterior wall velocity (Vpw) was calculated as:

$$\mathrm{Vpw\ (s^{-1})} = \frac{\mathrm{PWE}}{\mathrm{LVET} \times \mathrm{EDD}}$$

Similarly a normalised mean interventricular septal velocity (Vivs) was calculated as:

$$\mathrm{Vivs\ (s^{-1})} = \frac{\mathrm{IVSE}}{\mathrm{LVET} \times \mathrm{EDD}}$$

The ratio of left atrial to aortic root diameters (LA/Ao) was calculated for improved detection of left atrial enlargement (Brown *et al.*, 1974).

All the calculations were made using the average obtained from five cardiac cycles, excluding four patients who were in atrial fibrillation. In these patients an average of 10 cycles was used.

Normal values for these echocardiographic measurements were those obtained from a group of 14 closely matched healthy subjects with no clinical, radiological, or electrocardiographic evidence of cardiovascular abnormality.

Results

CLINICAL CHARACTERISTICS

Eleven male subjects and nine female subjects were studied, their ages ranged from 16 to 54 years, with a mean age of 31 years. Five patients were in class II (HYHA), 11 were in class III, and four were in class IV. The electrocardiogram was normal in only three patients. Four patients had atrial fibrillation, seven had left atrial enlargement, and eight patients had electrocardiographic evidence of right ventricular hypertrophy. None of the patients had clinical or laboratory evidence of rheumatic activity. In all patients the degree of mitral stenosis was judged to be severe enough to warrant mitral commissurotomy.

ECHOCARDIOGRAPHIC FINDINGS

Mitral valve echogram

All patients showed the classic findings of mitral stenosis (Feigenbaum, 1976). The E-F slope was flat in six patients, 10 mm/s or less in eight, and between 11 and 18 mm/s in six. The mitral valve excursion (C–E) ranged from 13 to 30 mm. It was less than 20 mm in nine patients and the mean value for the whole group was 22 mm.

Measurements

Table 1 shows the measured internal diameters of the right and the left ventricles, aortic root, and left atrium. The thickness and excursion of the septum and left ventricular posterior wall are shown in Table 2. Though the right ventricular internal diameter was greater and end-diastole was less in patients with mitral stenosis than in normal subjects, the changes were not statistically significant. However, the thickness of the left ventricular posterior wall was significantly reduced ($P < 0{\cdot}05$). In addition, the increase in left atrial dimension and decrease in aortic root dimension were significant ($P < 0{\cdot}001$). The extent of excursion of the posterior wall and interventricular septum was not very different from that in normal subjects.

Table 1 *Echocardiographic measurements*

Case no.	*RVD (cm)*	*EDD (cm)*	*AoRD (cm)*	*LAD (cm)*
1	1·3	4·8	2·9	3·8
2	0·9	4·4	2·6	4·8
3	1·0	4·4	2·6	4·8
4	1·7	4·9	3·3	5·0
5	1·6	5·0	2·5	3·8
6	3·1	4·5	1·9	4·5
7	1·1	4·4	2·9	4·4
8	—	—	1·9	3·8
9	—	—	2·5	4·1
10	2·5	3·9	2·3	3·6
11	2·1	4·1	—	3·8
12	—	5·0	3·1	3·1
13	1·9	4·4	1·9	4·4
14	4·0	3·8	1·9	3·8
15	2·0	—	2·5	4·4
16	2·8	4·4	2·5	—
17	1·9	4·0	1·9	5·0
18	—	4·5	2·4	4·8
19	1·9	4·4	2·1	4·4
20	2·1	5·0	2·4	4·8
Mean	2·0	5·4	2·4	4·3
SE	0·19	0·09	0·098	0·125
Normals (mean)	1·5	4·7	3·27	3·23
SE	0·12	0·102	0·064	0·062
P <	0·1	NS	0·001	0·001

RVD, right ventricular internal diameter; EDD, end-diastolic diameter of left ventricle; AoRD, aortic root diameter; LAD, left atrial diameter.

Indices of left ventricular performance

The cardiac output, stroke volume, ejection fraction, and normalised mean rate of circumferential fibre shortening (Vcf) were all reduced in patients with mitral stenosis, and the changes were significant (Table 3). Vcf was reduced by more than two standard errors (less than 1·10 circ/s) in 14 out of 17 patients, while the ejection fraction was reduced to less than 0·55 in about 50 per cent of patients. The mean values for the normalised velocities of the posterior wall (Vpw), interventricular septum (Vivs), and the maximum systolic and diastolic endocardial velocities were significantly lower in patients than in normal subjects (Table 4).

The changes in myocardial contractility expressed as Vcf were inversely related to both the internal right ventricular diameter ($r=-0{\cdot}767$, $P<0{\cdot}001$) (Fig. 3) and the degree of left atrial enlargement expressed as LA/Ao ratio ($r=-0{\cdot}554$, $P<0{\cdot}05$) (Fig. 4). The latter relation did not include case 12. A positive correlation was present between Vcf and the extent of posterior wall excursion ($r=0{\cdot}635$, $P<0{\cdot}01$) (Fig. 5) and the ejection fraction ($r=0{\cdot}847$, $P<0{\cdot}001$).

Clinical echocardiographic correlates

Fig. 6 and 7 show the extent of impairment of left

Table 2 *Echocardiographic measurements*

Case no.	*IVST (cm)*	*IVSE (cm)*	*LVT (cm)*	*PWE (cm)*
1	0·8	—	0·6	0·8
2	0·8	0·6	0·6	1·1
3	1·0	0·5	0·6	0·9
4	0·7	—	0·6	1·1
5	1·1	0·6	0·5	0·9
6	0·6	0·4	0·6	0·8
7	1·0	0·8	0·6	1·2
8	1·3	0·6	0·5	0·8
9	—	—	0·5	0·9
10	0·6	0·5	0·6	0·8
11	1·3	0·5	0·8	0·9
12	—	0·4	0·5	0·6
13	1·3	0·6	0·9	0·9
14	0·9	0·4	0·8	0·7
15	—	—	0·5	1·1
16	0·8	—	1·0	0·6
17	1·0	0·6	0·8	1·2
18	0·9	1·0	0·9	0·8
19	0·6	0·4	0·8	0·8
20	1·1	0·8	0·7	0·6
Mean	0·9	0·6	0·7	0·9
SE	0·058	0·045	0·036	0·042
Normals (mean)	0·8	0·6	0·8	1·2
SE	0·040	0·10	0·040	0·10
P <	NS	NS	0·05	0·1

IVST, interventricular septal thickness; IVSE, interventricular septal excursion; LVT, left ventricular posterior wall thickness; PWE, posterior wall excursion.

Table 3 *Indices of left ventricular function*

Case no.	*SV (ml)*	*CO (l/min)*	*EF*	*Vcf (circ/s)*
1	54	5·18	0·51	0·99
2	57	5·70	0·68	1·40
3	53	4·24	0·63	1·06
4	83	5·83	0·71	1·40
5	67	5·09	0·54	1·00
6	33	2·71	0·36	0·52
7	53	3·71	0·63	1·22
8	—	—	—	—
9	—	—	—	—
10	37	2·15	0·63	0·77
11	27	2·38	0·39	0·50
12	56	4·48	0·45	0·58
13	50	3·10	0·60	0·93
14	22	2·33	0·42	0·61
15	—	—	—	—
16	36	2·88	0·43	0·83
17	37	4·07	0·58	0·83
18	60	3·48	0·66	0·98
19	47	3·76	0·56	0·83
20	61	3·90	0·49	0·72
Mean	49	3·82	0·55	0·89
SE	3·76	0·197	0·030	0·067
Normals (mean)	72	5·02	0·74	1·26
SE	6·2	0·23	0·013	0·08
P <	0·001	0·001	0·001	0·001

SV, stroke volume; CO, cardiac output; EF, ejection fraction; Vcf, normalised mean rate of circumferential fibre shortening.

Table 4 *Indices of myocardial contractility*

Case no.	*Vpw* (s^{-1})	*Vivs* (s^{-1})	*MSEV* *(cm/s)*	*MDEV* *(cm/s)*
1	1·27	—	2·5	3·2
2	1·09	0·60	2·5	5·0
3	0·72	0·40	4·6	6·9
4	0·95	—	—	—
5	0·81	0·54	—	—
6	0·71	0·35	5·0	4·1
7	1·11	0·74	6·1	3·2
8	—	—	1·8	5·3
9	—	—	2·8	6·9
10	0·56	0·35	3·1	0·3
11	0·73	0·41	5·3	6·0
12	0·39	0·26	—	—
13	0·71	0·51	2·9	2·2
14	0·62	0·35	4·0	3·7
15	—	—	5·0	6·9
16	0·63	—	4·2	2·9
17	1·00	0·50	5·2	6·0
18	0·56	0·71	4·3	10·1
19	0·65	0·33	4·0	7·6
20	0·43	0·58	—	—
Mean	0·76	0·47	4·0	5·6
SE	0·056	0·039	0·308	0·579
Normals (mean)	0·95	0·61	6·2	18·0
SE	0·02	0·02	0·256	0·548
P <	0·005	0·005	0·001	0·001

Vpw, normalised velocity of the posterior wall; Vivs, normalised velocity of the interventricular septum; MSEV, maximum systolic endocardial velocity; MDEV, maximum diastolic endocardial velocity.

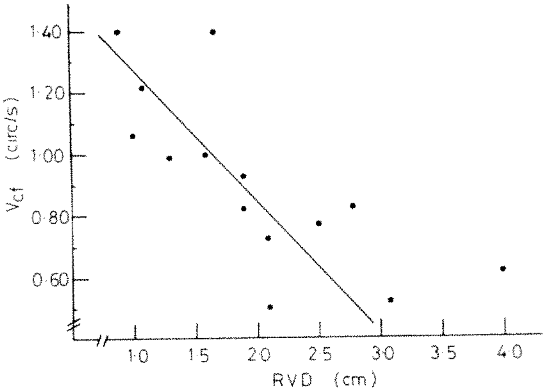

Fig. 3 *Relation between Vcf and right ventricular internal diameter. r=−0·767; P<0·001.*

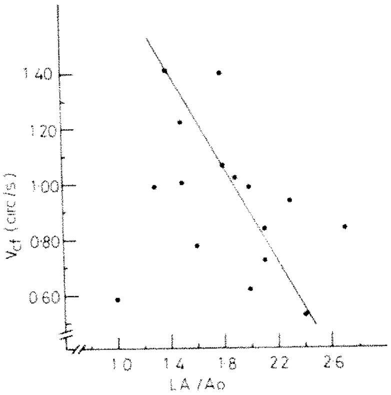

Fig. 4 *Relation between Vcf and the degree of left atrial enlargement expressed as LA/Ao ratio. r=−0·554; P<0·05. Case 12 is not included in the correlation.*

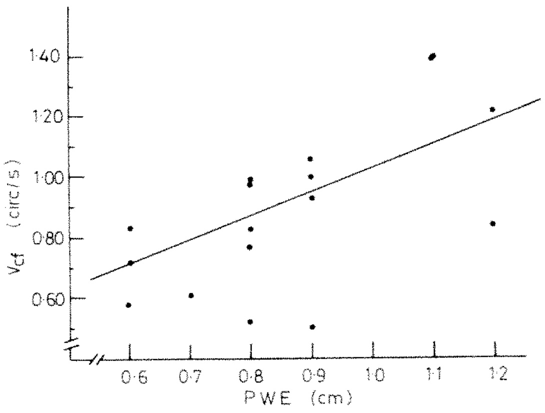

Fig. 5 *Relation between Vcf and the extent of posterior wall excursion. r=0·635; P<0·01.*

ventricular function expressed as changes in Vcf, EF, and Vpw in relation to the clinical severity of mitral stenosis (NYHA classification). Deterioration in left ventricular performance was greater in patients of class IV than in those of class II. Increase in right ventricular internal diameter progressed from patients in class II to patients in class IV (Fig. 7). Patients in class IV had the largest right ventricles.

Discussion

The high incidence of impairment in left ventricular function in our patients with mitral stenosis was at variance with previous reported incidences in other studies. Harvey *et al.* (1955) found an incidence of 13 per cent in their patients, while Kennedy *et al.* (1970) found that 37 per cent of patients with mitral stenosis had evidence of impaired myocardial contraction. In a recent echocardiographic study, McDonald (1976) found an incidence of 30 per cent. The very high incidence in our patients was not completely unexpected. Two factors might have been responsible; first, patients in our study had mitral stenosis necessitating cardiac surgery. In such a selected group of patients the degree of mitral stenosis and functional disability would be greater than in a random selection of patients present in other studies. Secondly, the severe and

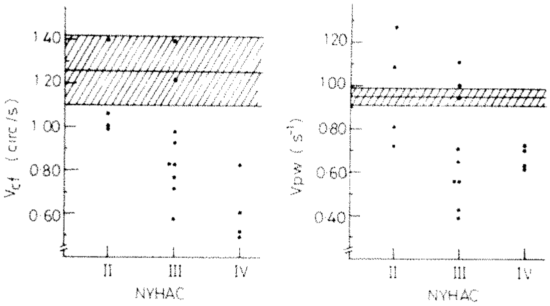

Fig. 6 *Clinical-echocardiographic correlates. Clinical severity of mitral stenosis (NYHA classification) and changes in Vcf and Vpw. The hatched area represents the mean values for the normals ± 2 standard errors.*

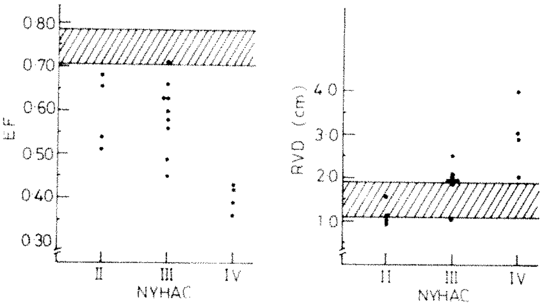

Fig. 7 *Clinical-echocardiographic correlates. Clinical severity of mitral stenosis (NYHA classification) and changes in ejection fraction (EF) and right ventricular internal diameter (RVD). The hatched area represents the normals ± 2 standard errors.*

florid nature of rheumatic fever, its early age of onset, and the significant haemodynamic burden in Egyptian patients is different from that in western countries (El-Sherif, 1975). Botros and Sabaa (1976) in a haemodynamic study of 32 young Egyptian patients with mitral stenosis have shown that the pulmonary arterial pressure approached systemic level in 50 per cent of their patients. This figure was 13 per cent in Wood's series (Wood, 1954). The cardiac index was reduced in all patients in the Egyptian series, ranging between 2 and 2·5 l/min per m^2.

Indices of left ventricular performance, viz. Vcf, ejection fraction, Vpw, and stroke volume were reduced in patients with mitral stenosis. The impairment in left ventricular function was related to the degree of functional disability (NYHA), right ventricular dilatation, and left atrial enlargement.

In a disease like mitral stenosis where the haemodynamic burden of the mechanical obstruction is on the pulmonary circulation and right ventricle it was unusual to find a relation between left ventricular dysfunction and clinical disability. This suggests that some of the symptoms experienced by patients with mitral stenosis may be the result of impairment in left ventricular function. The inverse relation between Vcf and right ventricular internal diameter ($r = -0.767$; $P < 0.001$) (Fig. 3) and the degree of left atrial enlargement (LA/Ao ratio) ($r = -0.554$, $P < 0.05$) favours the assumption that the impairment of left ventricular contractility was also related to the severity of mitral stenosis reflected in left atrial and right ventricular dilatation. On the other hand, hypokinesis of the left ventricular wall was found by Curry *et al.* (1970) not only in patients with mitral stenosis but also in patients with right ventricular enlargement not secondary to mitral valve disease.

Subtle changes in left ventricular contraction have been reported in mitral stenosis by Heller and Carleton (1970). Of their 25 patients, 20 showed distortion, immobility, and regidity of the posterobasal area of the left ventricle. Similarly, localised abnormalities in the wall of the left ventricle have been described by Horwitz *et al.* (1973). Fibrosis in or near the papillary muscles was postulated as a possible cause. However, the reduction in our patients of the mean values for the normalised velocities of the posterior wall (Vpw), interventricular septum (Vivs), and the maximum systolic (MSEV) and diastolic (MDEV) endocardial velocities are consistent with the view that a generalised abnormality of myocardial mechanical performance is responsible for the occurrence of left ventricular dysfunction in some patients with mitral stenosis. Holzer *et al.* (1973) found abnormalities of ventricular contraction in 10 patients with rheumatic mitral stenosis.

The present study suggests that abnormalities in contractility of the left ventricular myocardium can be responsible for the impaired myocardial function in patients with mitral stenosis and that such impairment is clinically significant. It may be a contributing factor in some patients who have an unsatisfactory clinical response to mitral commissurotomy. Histopathological studies in patients with mitral stenosis showed that the failure of improvement after mitral commissurotomy was related to the extent of myocardial involvement by the rheumatic process (Selim, 1976).

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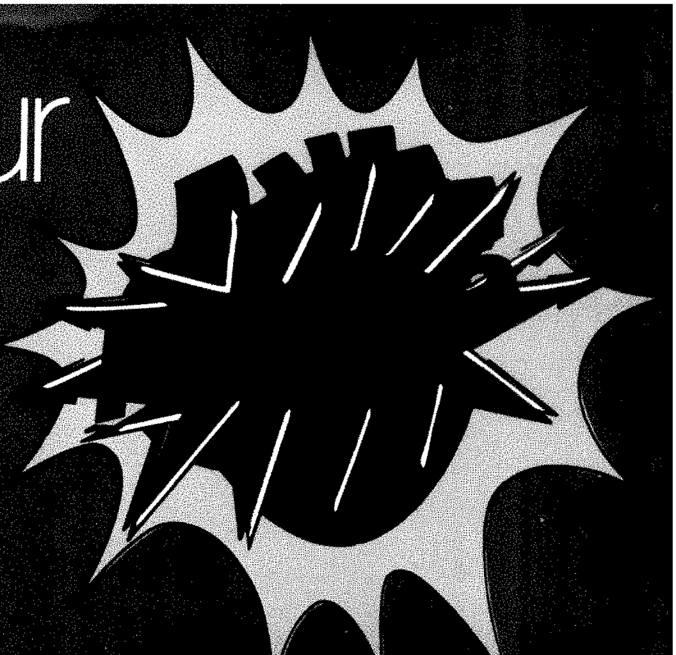

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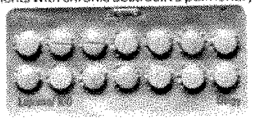

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Ventricular response to isometric and isotonic exercise[1]

Echocardiographic assessment

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SUMMARY The effects of supine isometric handgrip and graded isotonic bicycle ergometer exercise on left ventricular performance were studied echocardiographically in 20 normal subjects, aged 18 to 36. Measurements of the left ventricular minor axis diameter were taken from recordings performed at rest, during each form of exercise, and during recovery. At the completion of isometric exercise, the pressure-rate product increased significantly. There was no significant change in percentage of fractional shortening (%△D), while there was a small but significant fall in peak velocity of circumferential fibre shortening (peak Vcf).

Isotonic exercise resulted in a significant increase in %△D and peak Vcf. The pressure-rate product also increased and showed a positive correlation with peak Vcf.

Isotonic exercise produced a much greater stimulus to left ventricular contractility than isometric exercise and may be a useful means of detecting latent left ventricular dysfunction echocardiographically.

The echocardiogram can provide a useful assessment of left ventricular performance in patients with disease processes that affect the ventricle in a uniform fashion. This technique measures stroke volume, ejection fraction (Pombo *et al.*, 1971; Fortuin *et al.*, 1972), percentage of fractional shortening (McDonald *et al.*, 1972; Stack *et al.*, 1976), mean velocity of circumferential fibre shortening (Paraskos *et al.*, 1971; Cooper *et al.*, 1972; Fortuin *et al.*, 1972), and peak velocity of circumferential fibre shortening (Paraskos *et al.*, 1971; Gibson and Brown, 1973; Quinones *et al.*, 1975; Boughner *et al.*, 1976). These measurements readily detect severe left ventricular dysfunction but mild dysfunction may produce few measurable changes at rest. We undertook this study to determine the potential value of incorporating exercise as a part of the echocardiographic evaluation. Two forms of exercise stress testing lend themselves to echocardiographic assessment: (a) supine isometric handgrip exercise (Stefadourous *et al.*, 1974a) and (b) supine isotonic bicycle ergometer exercise (Stein *et al.*, 1978).

Subjects and method

The study population consisted of 20 healthy volunteers (age 18 to 36; eight women, 12 men). All were considered to be normal on the basis of history, physical examination, and 12 lead electrocardiogram. None of the subjects was taking any medications.

ECHOCARDIOGRAPHY

The echocardiograms were obtained using a Unirad, Series C echocardiograph unit equipped with a Honeywell 1858 strip chart recorder. Patients were studied in the slight left lateral position with the transducer positioned in the fourth or fifth left intercostal space. The left ventricular minor axis diameter was recorded by directing the ultrasound beam just inferior to the mitral valve and recordings were made at a paper speed of 100 mm/s. Care was taken to avoid alterations in transducer position during the study, thus avoiding spurious changes of left ventricular dimensions. Subjects were also instructed to avoid performing the Valsalva manoeuvre and were carefully observed for this.

ISOMETRIC EXERCISE PROCEDURE

Isometric handgrip exercise was performed using

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a Stoelting dynamometer. Brachial blood pressure was measured using a Cardy-8 sphygmomanometer.

Supine resting measurements of blood pressure and heart rate were obtained and the resting left ventricular echocardiogram was recorded. Each subject was then asked to perform three minutes of supine isometric exercise at 30 per cent of the individual's predetermined peak grip strength. Simultaneous recordings of the left ventricular dimensions (approximately 10 seconds in duration), blood pressure, and heart rate were made at one-minute intervals during exercise. After handgrip exercise, similar recordings were made at one-minute intervals for two minutes during which time full recovery occurred.

ISOTONIC EXERCISE PROCEDURE

After an additional five minutes of rest, a further set of resting recordings were made. Isotonic exercise was then performed using a Siemens-Elema bicycle ergometer system mounted vertically at the foot of the bed. Each subject was asked to perform six minutes of supine bicycle ergometer exercise at loads of 25, 50, 75, 100, 125, and 150 watts, the load being increased at one-minute intervals. Recordings of the left ventricular dimensions, blood pressure, and heart rate were made at one-minute intervals during exercise and at two, four, and eight minutes after exercise, during which time complete recovery occurred.

Although total cardiocirculatory adaptation to any magnitude of exertion does not occur for two to three minutes (Astrand and Rodahl, 1977), it was technically difficult to obtain adequate quality left ventricular echocardiograms throughout a graded exercise procedure using three-minute stages. Since the cardiovascular adjustments to a submaximal workload reach a nearly steady state within the first minute of isotonic exercise (Donald *et al.*, 1955; Jones and Reeves, 1968; Van Citters and Franklin, 1969; Xenakis *et al.*, 1975), we elected to increase the workload at one-minute intervals during the bicycle exercise.

MEASUREMENTS AND CALCULATIONS

Analysis of the instantaneous left ventricular dimension and calculation of its peak rate of change was performed using a Hewlett-Packard Model 1838 desk top computer, a model 986A digitiser, and x-y plotter combination by a method modified from that of Gibson and Brown (1973). The recordings of the left ventricular echograms were placed on a digitising table and the endocardial echoes of the septum and posterior wall were digitised beginning at the onset of the R wave and ending with the T wave. The computer noted the position of these two echoes and automatically derived the instantaneous left ventricular diameter. It normalised this diameter measurement by dividing by the initial diameter, and this ratio was then displayed by the x-y plotter as a 'displacement ratio' versus time (Fig. 1). Peak Vcf was obtained manually by calculating the slope of the tangent to the mid portion of this curve, thus providing the normalised peak Vcf in circumferences per second. We decided to calculate peak Vcf in this fashion rather than having the computer calculate the instantaneous first derivative of the left ventricular diameter curve as described by other investigators (Gibson and Brown, 1973; Decoodt *et al.*, 1976) because we found that the normalised instantaneous diameter curve or 'displacement ratio' contained sufficient noise (produced by 'hand-shake' when tracing the echo) to make such a computer estimate of peak Vcf poorly reproducible. Such irregularities could be easily compensated for by the manual method resulting in a high degree of reproducibility for the peak Vcf estimate. The computer also calculated automatically the percentage of fractional shortening:

$$\frac{\mathrm{EDD} - \mathrm{ESD}}{\mathrm{EDD}} \times 100 \text{ (McDonald \textit{et al.}, 1972).}$$

The pressure-rate product was obtained by multiplying the systolic blood pressure (mmHg) by the heart rate (beats/min).

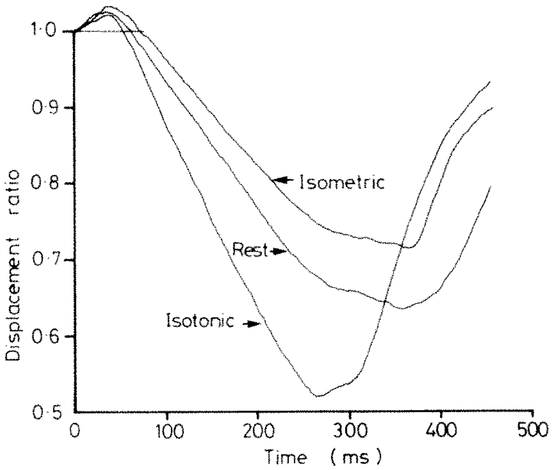

Fig. 1 *Computer plot of the displacement ratio versus time curves corresponding to the ventricular echograms of a normal subject (see Fig. 2) at rest, during three minutes of isometric exercise, and during six minutes of isotonic exercise. The slope of the mid portion of each curve provided the respective normalised peak Vcf in circ/s (displacement ratio = instantaneous left ventricular diameter divided by end-diastolic diameter).*

All measurements were taken from recordings taken at rest (Fig. 2a), at one-minute intervals during isometric exercise (Fig. 2b), and during a two-minute recovery period. They were also made from recordings taken just before the initiation of isotonic exercise, at one-minute intervals during isotonic exercise (Fig. 2c), and at two, four, and eight minutes after exercise.

Measurements of four beats at each of these time intervals were carried out to establish the degree of beat-to-beat and interobserver variation in the ventricular function indices. These were performed for 48 sets of beats in four randomly selected patients. We found the coefficients of variation for percentage of fractional shortening to be 8 per cent and for peak Vcf to be 3 per cent. This indicated good reproducibility since the coefficient of variation was well below the 12 per cent level (England, 1975). It was not possible to obtain and measure this ideal number of cardiac cycles from the eight to 10 second long tracings at each time interval in all 20 subjects. Therefore we selected a single cardiac cycle at each time interval in which the endocardial surfaces of the septum and the posterior left ventricular wall just inferior to the valve were clearly seen as continuous echoes throughout systole and diastole. In order to avoid the small changes of left ventricular dimensions with respiration during isotonic exercise, measurements were made only during expiration when the endocardial surfaces were clearly seen. During inspiration, those endocardial surfaces were often indistinct.

Statistical analysis was carried out using paired data comparison and Student's t test. Regression analysis was carried out by two variable analyses.

Results

RESTING

No significant difference was shown between resting left ventricular function indices before and after exercise. These are listed in Tables 1 and 2 and all values were within normal published ranges (Paraskos *et al.*, 1971; McDonald *et al.*, 1972; Quinones *et al.*, 1975; Boughner *et al.*, 1976).

ISOMETRIC EXERCISE

Three minutes of isometric handgrip exercise resulted in a significant ($P < 0{\cdot}001$) increase in blood pressure, heart rate, and the pressure-rate product. The systolic blood pressure rose 32 (±15) mmHg (mean ±1 SD) and heart rate 23 (±14) beats/min (mean ±1 SD). No significant change in percentage of fractional shortening occurred. However, the peak Vcf showed a small but significant decrease from 1·80±0·27 (mean ±1 SD) circumferences/s to 1·61±0·22 (mean

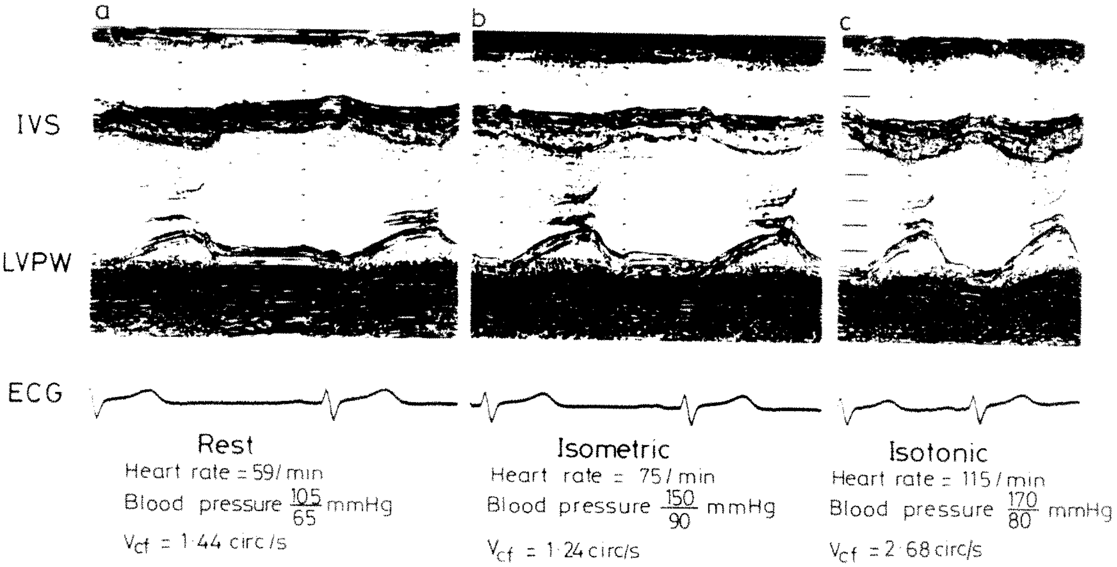

Fig. 2 *Left ventricular echogram of a normal subject, paper speed 100 mm/s* (a) *at rest,* (b) *during three minutes of isometric handgrip exercise, and* (c) *during six minutes of supine bicycle ergometer exercise. Note the minor fall in peak Vcf with isometric exercise and the distinct increase with isotonic exercise. IVS, interventricular septum; LVPW, left ventricular posterior wall; ECG, electrocardiogram; Vcf, peak velocity of circumferential fibre shortening.*

Table 1 *Echocardiographic variables during isometric exercise (mean ±SD)*

		Isometric exercise			Recovery	
	Rest	1 min	2 min	3 min	4 min	5 min
p Vcf (circ/s)	1·80	1·78	1·56	1·61*	1·63	1·81
	± 0·27	± 0·33	± 0·21	± 0·22	± 0·19	± 0·35
Percentage of fraction shortening	37	36	34	35	36	38
	± 4	± 6	± 5	± 6	± 4	± 6
End-diastolic diameter (mm)	50	50	51	51	51	51
	± 5	± 5	± 5	± 5	± 5	± 5
Heart rate (beat/min)	58	68	78	79**	57	59
	± 8	± 15	± 15	± 15	± 9	± 9
Systolic blood pressure (mmHg)	122	137	148	154**	124	122
	± 13	± 16	± 19	± 15	± 14	± 12
BP × HR (× 10³)	7·0	10·5	12·1	12·4**	7·1	7·1
	± 1·1	± 2·5	± 3·0	± 3·0	± 1·3	± 1·4

Note: Significant differences from resting values at completion of exercise are indicated by *P < 0·01 and **P < 0·001.
Vcf, velocity of circumferential fibre shortening; HR × BP, systolic pressure-rate product.

Table 2 *Echocardiographic variables during supine bicycle ergometer exercise and recovery*

		Isotonic exercise						Recovery		
	Rest	1 min	2 min	3 min	4 min	5 min	6 min	8 min	10 min	14 min
p Vcf (circ/s)	1·78	1·83	2·04	2·13	2·29	2,49	2·89**	1·96	1·73	1·87
	± 0·21	± 0·27	± 0·30	± 0·28	± 0·34	± 0·32	± 0·22	± 0·22	± 0·28	± 0·35
Percentage of fraction shortening	36	38	41	43	44	44	46**	42	38	37
	± 5	± 5	± 6	± 6	± 4	± 5	± 6	± 4	± 4	± 5
End-diastolic diameter (mm)	50	51	51	51	51	51	50	52	52	50
	± 5	± 5	± 5	± 5	± 6	± 6	± 6	± 6	± 6	± 6
Heart rate (beats/min)	66	90	99	108	115	123	130**	78	68	69
	± 13	± 12	± 11	± 12	± 14	± 18	± 14	± 22	± 14	± 17
Systolic blood pressure (mmHg)	124	138	144	152	161	173	183**	138	121	122
	± 12	± 15	± 15	± 17	± 18	± 18	± 17	± 13	± 11	± 15
HR × BP (× 10³)	8·1	12·3	14·3	16·4	18·4	21·2	22·9**	10·5	7·6	8·2
	± 1·5	± 2·1	± 1·9	± 2·4	± 2·6	± 3·0	± 3·0	± 3·9	± 2·3	± 1·3

Note: Significant differences from resting values at completion of exercise are indicated by **P < 0·001.
Vcf, velocity of circumferential fibre shortening; HR × BP, systolic pressure-rate product.

±1 SD) circumferences/s (P < 0·01, Table 1 and Fig. 3a).

ISOTONIC EXERCISE

Six minutes of isotonic exercise resulted in a pronounced rise in heart rate and blood pressure with a significant (P < 0·001) increase in the pressure-rate product to a value nearly twice that produced by isometric exercise. The percentage of fractional shortening and peak Vcf (Table 2 and Fig. 3b) rose significantly (P < 0·001).

Linear regression analysis showed a positive correlation between the peak Vcf and the pressure-rate product during isotonic exercise (r = 0·71, N = 128, P < 0·001) with a standard error of the estimate of ±0·34 (Fig. 4). However, no such correlation was demonstrated for these variables during isometric exercise (r = 0·14).

Discussion

The cardiovascular responses to isometric and isotonic exercise differ in several important ways. Within seconds of initiating isometric handgrip exercise, the heart rate begins to increase (Freyschuss, 1970; Petro *et al.*, 1970; Nutter *et al.*, 1972) apparently resulting from the withdrawal of vagal influences on the heart (MacDonald *et al.*, 1966; Nutter *et al.*, 1972). The degree of response is not related to the bulk of muscle involved in the isometric contraction and the exact mechanism by which these changes occur is not fully understood (Lind *et al.*, 1964; Nutter *et al.*, 1972). End-diastolic volume (preload) (Grossman *et al.*, 1973; Stefadourous *et al.*, 1974b) and end-diastolic pressure (Kivowitz *et al.*, 1971; Grossman *et al.*, 1973) do not change. Stroke volume also does not change significantly (Grossman, 1974). Cardiac output increases as a result of the tachycardia and, since the systemic vascular resistance remains unchanged (Stefadourous *et al.*, 1974b), the arterial pressure increases. An increase in myocardial contractility has been postulated to maintain stroke volume in the presence of an unchanged preload and increased afterload (Helfant *et al.*, 1971; Nutter *et al.*, 1972; Grossman *et al.*, 1973; Stefadourous *et al.*, 1974a).

Isotonic exercise also results in an immediate

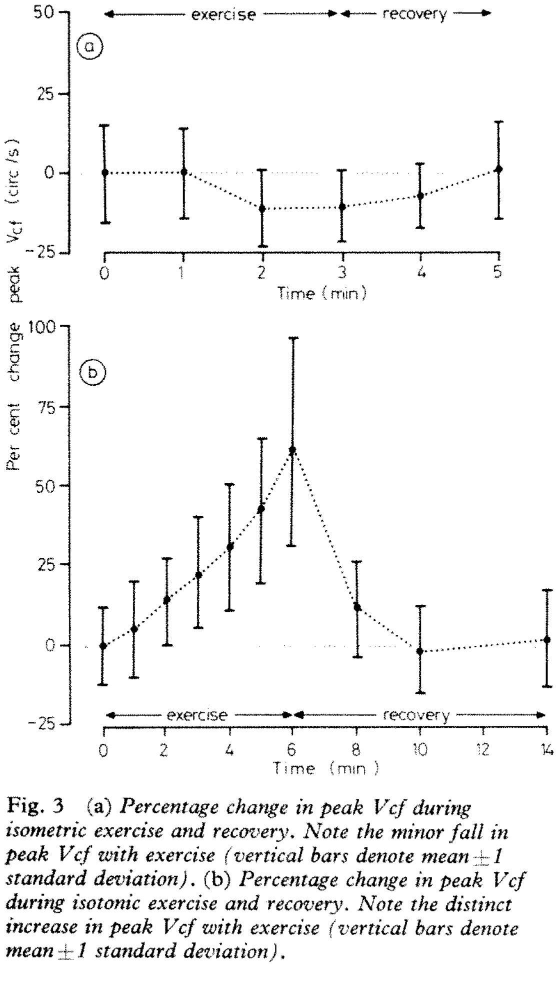

Fig. 3 (a) *Percentage change in peak Vcf during isometric exercise and recovery. Note the minor fall in peak Vcf with exercise (vertical bars denote mean ± 1 standard deviation).* (b) *Percentage change in peak Vcf during isotonic exercise and recovery. Note the distinct increase in peak Vcf with exercise (vertical bars denote mean ± 1 standard deviation).*

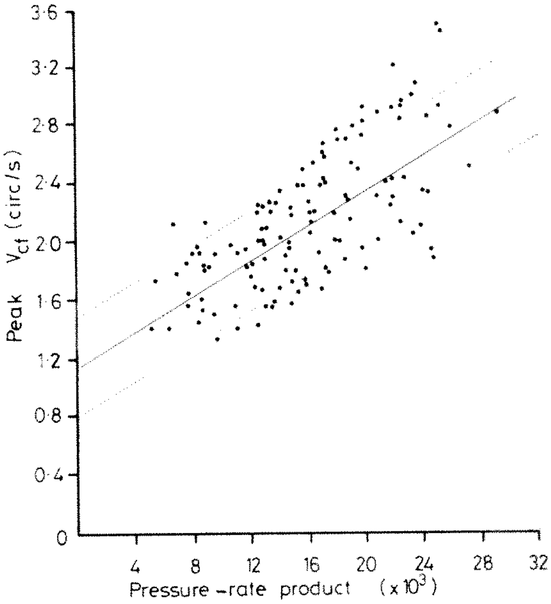

Fig. 4 *The linear correlation between peak Vcf and pressure-rate product during isotonic exercise. The regression line for the 20 subjects is indicated by the solid line while the dotted lines indicate one standard error of the estimate.*

increase in heart rate (Donald *et al.*, 1955; Xenakis *et al.*, 1975). In the supine position, preload does not change (Rushmer, 1959), myocardial contractility increases, and cardiac output rises (Marshall and Shepherd, 1968). Stroke volume in the resting supine position seems to be at or near the maximal level reached during heavy work, and exercise in this position produces little or no increase in stroke volume (Rushmer, 1959). This differs from the erect posture in which the end-diastolic volume and stroke volume are lower at rest (Rushmer, 1976). These lower values are restored to approximately those of the recumbent position with even the mildest exercise and heavy exertion produces only modest additional increases (Rushmer, 1976).

Our results show the distinct differences between the cardiac response to isometric and isotonic exercise and illustrate the ease with which they may be detected echocardiographically. With isometric exercise, we observed no alteration in end-diastolic diameter on the echocardiogram, a finding that is consistent with previous reports (Stefadourous *et al.*, 1974a). In contrast to those reports, we recorded a slight fall in the percentage fractional shortening and a small statistically significant fall in the velocity of circumferential fibre shortening. This would be consistent with previous observations where Vcf was found to be inversely related to ventricular afterload (Quinones *et al.*, 1975). However, the failure of peak Vcf to fall much during isometric exercise suggests that myocardial contractility increased sufficiently to almost maintain the resting contraction velocities.

In contrast, supine isotonic exercise produced a pronounced increase in the velocity of circumferential fibre shortening, indicating a major augmentation in myocardial contractility. We observed no change in the end-diastolic diameter, implying that an alteration in preload did not play a significant part in this increased contraction velocity (Rushmer, 1959; Stein *et al.*, 1978). Percentage fractional shortening rose significantly as would be expected.

It has been suggested that isometric exercise at 25 to 50 per cent of maximum voluntary contraction when performed during cardiac catheterisation can be useful in detecting latent left ventricular dysfunction (Helfant *et al.*, 1971; Kivowitz *et al.*, 1971; Grossman *et al.*, 1973; Grossman, 1974). An abnormal end-diastolic pressure may be produced during such exercise or, in patients in whom the ventricular end-diastolic pressure is already raised, a further increase may be produced. However, our results indicate that isometric exercise at 30 per cent of maximum voluntary contraction is unlikely to produce a sufficiently dramatic change in contractility to be a useful part of the echocardiographic assessment of left ventricular function. Though a severely diseased ventricle might be expected to show a definite fall in myocardial contraction velocity under these circumstances, a ventricle with borderline dysfunction might not.

In contrast, isotonic exercise produces a dramatic stimulus to myocardial contractility and would be a more suitable provocative test for uncovering latent left ventricular dysfunction as determined by echocardiography.

Although we were able to obtain satisfactory recordings during isotonic exercise in all of the relatively young individuals studied, it may not be possible to achieve the same degree of success in older patients or in those with some degree of emphysema.

CLINICAL IMPLICATIONS

This study has shown that echocardiographic assessment of left ventricular function in normal subjects during both supine isometric and isotonic exercise is practical. Whereas isometric exercise has little measurable effect on left ventricular performance, isotonic exercise produces a dramatic and easily measurable stimulus to myocardial contractility and may be a useful means of detecting left ventricular dysfunction in disease processes that affect the left ventricle in a uniform fashion.

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Spectrum of echocardiographic findings in tricuspid valve endocarditis

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SUMMARY This report describes a spectrum of M-mode and cross-sectional echocardiographic abnormalities in eight patients with infective endocarditis of the tricuspid valve. The M-mode echocardiogram of the tricuspid valve was abnormal in all but one patient in whom abnormal echoes were seen anterior to the tricuspid valve, in the right ventricular cavity and right ventricular outflow tract. Six patients had shaggy echoes on the tricuspid valve; and one patient showed multilayered echoes on the tricuspid valve which resembled a right atrial myxoma. Irregular diastolic fluttering of the tricuspid valve, indicative of ruptured chordae tendineae, was noted in three patients.

The cross-sectional echocardiogram showed abnormal thick shaggy echoes on the tricuspid valve in all five patients on whom the procedure was performed. Contrast echocardiography confirmed the presence of tricuspid regurgitation in four patients.

We conclude that echocardiography is useful in the diagnosis of tricuspid valve vegetations, and in detecting complications such as ruptured chordae tendineae and tricuspid regurgitation.

Several reports have outlined the usefulness of echocardiography in the diagnosis of infective endocarditis of the aortic and mitral valves (Dillon *et al.,* 1973; DeMaria *et al.,* 1975; Wray, 1975). Though echocardiographic diagnosis of tricuspid valve endocarditis has been described, the spectrum of abnormalities that may be seen on the echogram in this condition has not been clearly delineated (Lee *et al.,* 1974; Kisslo *et al.,* 1976a; Andy *et al.,* 1977; Thomson *et al.,* 1977). This report describes a variety of M-mode and cross-sectional echocardiographic findings that were observed in patients with infective endocarditis of the tricuspid valve.

Subjects and methods

Echocardiography was performed on eight patients with clinical and bacteriological evidence of infective endocarditis. Six patients gave a history of intravenous drug abuse. The source of infection in the other two patients was an infected antecubital cut-down site, and an infection after an operation on the large bowel, respectively. A grade 2–3/6 systolic murmur was heard at the left sternal border in five patients, only one of whom had the characteristic jugular venous pulse and hepatic pulsations suggestive of tricuspid regurgitation.

The diagnosis was confirmed at the time of operation in two patients whose infection was resistant to antibiotic therapy. In one patient a large finger-like vegetation was removed without damage to the tricuspid valve, and the other had excision of the tricuspid valve.

M-mode echocardiography was performed on all patients, using an Ekoline 20 ultrasonoscope, a 2·25 MHz, 0·5 inch, 7·5 cm focus transducer, and a Honeywell 1856 recorder. Cross-sectional echocardiography was done on five patients, using a SKI 30° mechanical sector scanner. Echograms of the long axis and short axis of the heart were obtained from the left sternal border, and a hemiaxial view recorded from the cardiac apex (Kisslo *et al.,* 1976b). In these five patients, 10 ml saline were injected into a peripheral vein, while the right atrium and right ventricle were being visualised simultaneously by cross-sectional echocardiography (DeMaria *et al.,* 1978; Lieppe *et al.,* 1978).

Results

M-MODE ECHOCARDIOGRAPHY

The tricuspid valve was abnormal in all but one

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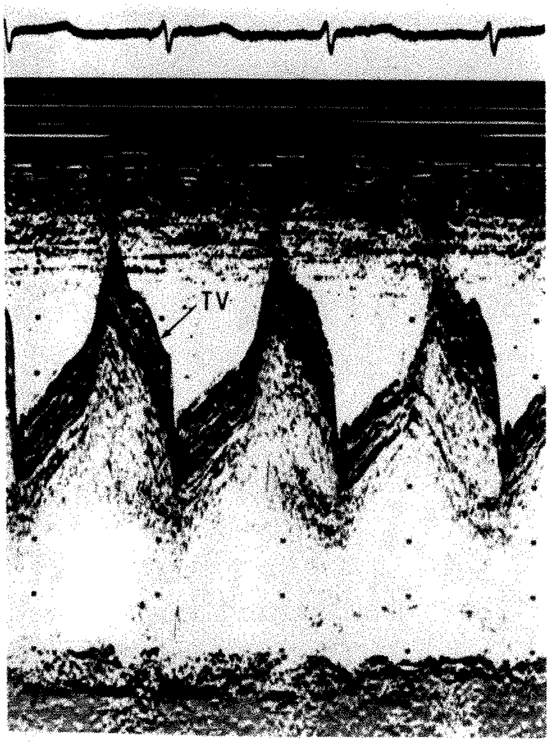

Fig. 1 *Echocardiogram illustrating shaggy echoes on the tricuspid valve (TV) consistent with vegetations on the anterior leaflet of the tricuspid valve.*

patient. Shaggy echoes were noted on the tricuspid valve in six patients (Fig. 1 and 2). Multilayered echoes were seen on one patient (Fig. 3). The main body of the tricuspid valve was normal in one patient who, at operation, had a long finger-like vegetation attached to the base of the valve. Abnormal echoes which probably represented the tricuspid vegetation were noted anterior to the tricuspid valve, in the right ventricular cavity, and right ventricular outflow tract (Fig. 4 and 5). These abnormal echoes were not present in the echocardiogram performed after resection of the tricuspid vegetation (Fig. 6).

Irregular diastolic fluttering of the tricuspid valve, indicative of ruptured chordae tendineae, was noted in three patients (Fig. 7). There was no clinical evidence of pulmonary regurgitation in these patients.

CROSS-SECTIONAL ECHOCARDIOGRAPHY

The cross-sectional echogram was abnormal in all five patients on whom the procedure was performed. The cusps of the normal tricuspid valve appear as thin linear echoes. In contrast, our patients had thick shaggy echoes on the tricuspid valve (Fig. 8). In one patient besides a large vegetation on the septal leaflet of the tricuspid valve, another much smaller vegetation, which showed high frequency fluttering, was noted. The patient who had multilayered echoes resembling a myxoma showed dense echoes on the tricuspid valve and no mass was noted in the right atrium.

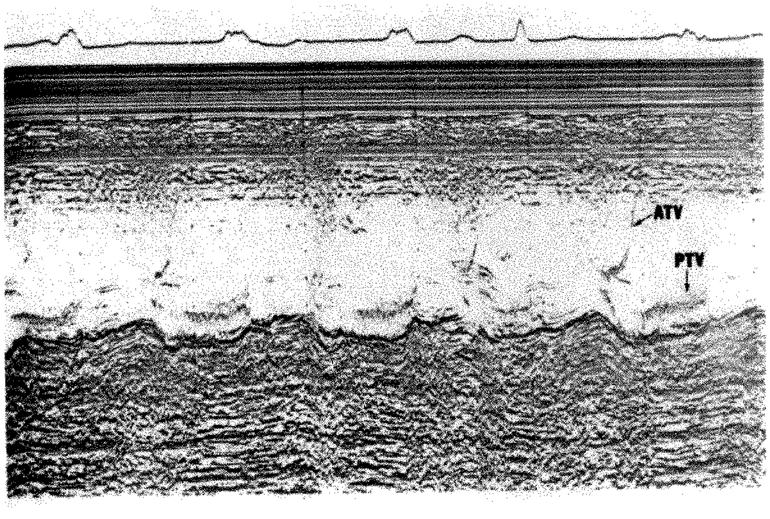

Fig. 2 *Echocardiogram illustrating shaggy echoes caused by vegetations on the posterior leaflet of the tricuspid valve (PTV). ATV, anterior leaflet of tricuspid valve.*

CONTRAST ECHOCARDIOGRAPHY

Injection of saline into a peripheral vein is followed by the appearance of micro-cavitations ('bubbles') in the right atrium and then in the right ventricle. In the normal subject these echoes disappear in five to six beats. In patients with tricuspid regurgitation the micro-cavitations move back and forth from the right ventricle to the right atrium and they persist for a much longer period of time (DeMaria *et al.*, 1978; Lieppe *et al.*, 1978). The micro-cavitations ('bubbles') are also seen in the inferior vena cava suggesting reversal of blood flow because of tricuspid regurgitation. Contrast echocardiography showed appearances suggesting tricuspid regurgitation in four of the five patients; all four had a systolic murmur though only one had a characteristic jugular venous pulse.

Discussion

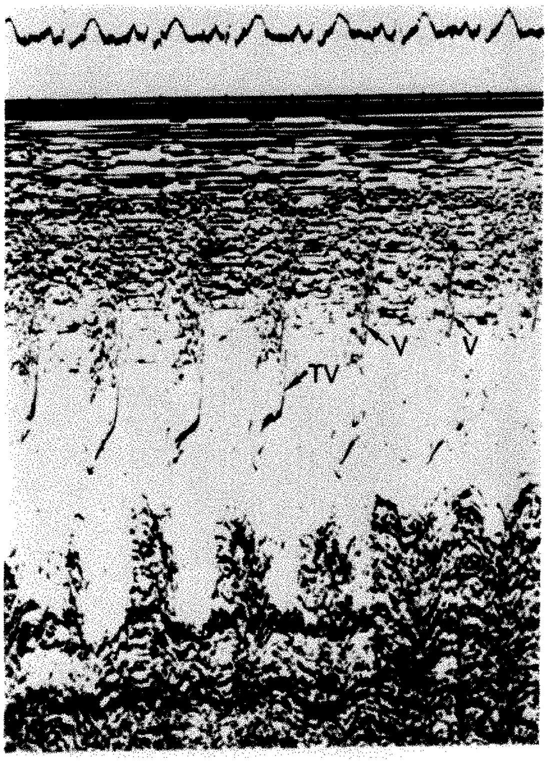

Fig. 4 *Echogram of a patient who had a vegetation on the tricuspid valve proven at surgery. Note that the tricuspid valve appears normal, because the echo-beam probably did not transect the area of the valve where the vegetation was attached. There is an abnormal echo (V) anterior to the valve which probably represents the vegetation.*

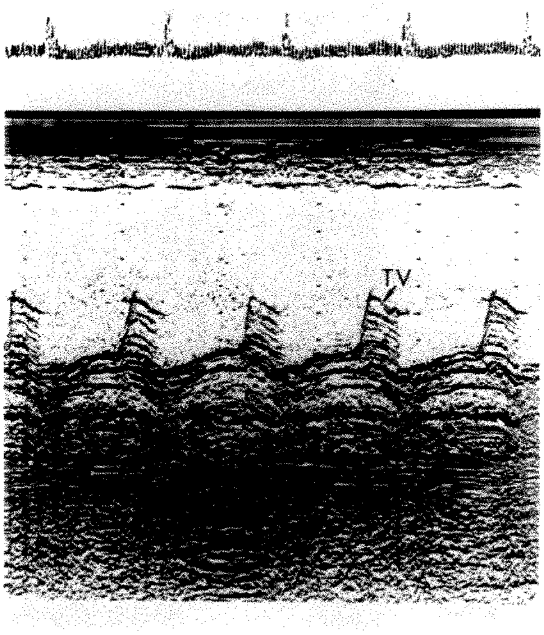

Fig. 3 *Echocardiogram shows layering of echoes on the tricuspid valve (TV) caused by vegetations. This echo could have been misinterpreted as a right atrial myxoma.*

Characteristic echocardiographic findings have been described in aortic and mitral valve endocarditis (Dillon *et al.*, 1973; DeMaria *et al.*, 1975; Wray, 1975). Shaggy diastolic echoes on the valve leaflets are typical of valvular vegetations. Other echocardiographic abnormalities are attributable to cusp or chordal rupture (Feigenbaum, 1973). All except one of our patients had abnormal tricuspid valve echograms. Shaggy echoes on the tricuspid valve were the commonest abnormality noted. One of our patients had multilayered echoes on the tricuspid valve, which could have been misinterpreted as a right atrial myxoma. The tricuspid valve echogram was normal in a patient who had a long finger-like vegetation arising from the base of the tricuspid valve. The vegetation was noted to protrude into the right ventricular outflow tract at surgery. Abnormal echoes were noted anterior to the tricuspid valve, in the right ventricle, and right ventricular outflow tract of this patient. This case illustrates the importance of scanning the right ventricle and right ventricular outflow tract in patients suspected of having infective endocarditis of the tricuspid valve. No such echoes have been seen in patients without endocarditis. Irregular diastolic fluttering of the tricuspid valve which suggested chordal rupture was observed in three patients. This indicates that besides diagnosing tricuspid valve vetegations, progressive damage to the valve can be assessed by echocardiography.

The cross-sectional echocardiogram was abnormal in all five patients on whom studies were performed. While the M-mode echogram permits diagnosis of valvular vegetations, the cross-sectional echocardiogram enables assessment of the size and extent of vegetations. In one patient the cross-sectional echogram showed a large vegetation on the septal leaflet of the tricuspid valve, and another much smaller vegetation which demonstrated high frequency fluttering. Since in our experience, as well as in the experience of others, successful medical management is accompanied by persistence of the abnormal echocardiogram in most instances, the ability to detect a new vegetation on a valve and hence recurrence of endocarditis, is a potential application of cross-sectional echocardiography. The cross-sectional echogram was also useful in ruling out a right atrial myxoma in a patient whose M-mode echogram showed multilayered echoes on the tricuspid valve which resembled a myxoma.

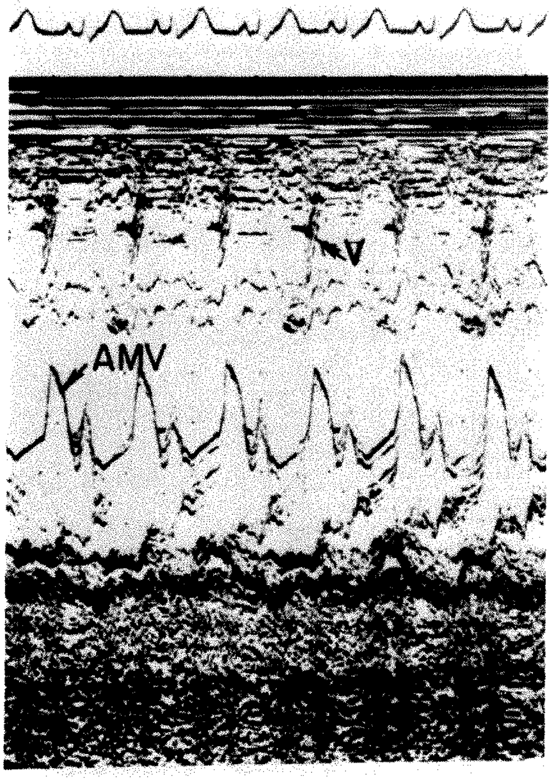

Fig. 5 *Echocardiogram of the right ventricle in the patient referred to in Fig. 4. Abnormal shaggy echoes (V) which represent the vegetation are seen in the right ventricular cavity. AMV, anterial mitral leaflet.*

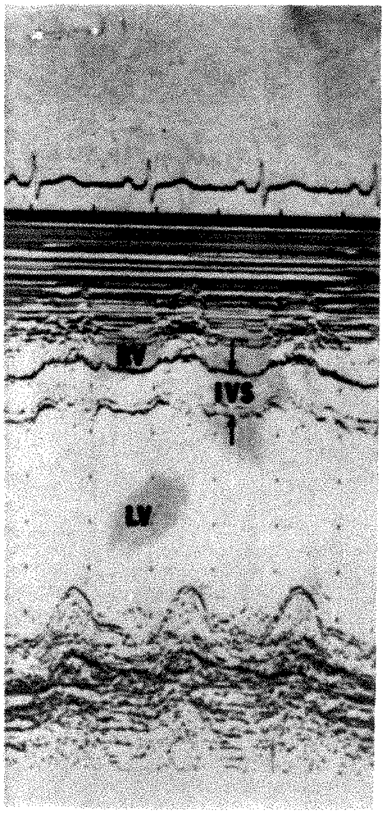

Fig. 6 *Echogram of patient referred to in Fig. 4 recorded after resection of a tricuspid vegetation. The abnormal echo in the right ventricle (RV) is no longer present. IVS, interventricular septum; LV, left ventricular cavity.*

Injection of saline into a peripheral vein while simultaneously recording the echocardiogram of the right atrium and right ventricle has been shown to be a reliable non-invasive method of diagnosing tricuspid regurgitation (DeMaria *et al.*, 1978; Lieppe *et al.*, 1978). The diagnosis of tricuspid regurgitation at the bedside may be particularly difficult in patients who have normal or low right ventricular pressures ('low pressure' tricuspid regurgitation) since the classical triad of a holosystolic murmur, prominent 'V' waves in the jugular venous pulse, and hepatic pulsations, may not be present in this setting (Wooley and Fontana, 1975). Only one of the four patients with positive contrast studies for tricuspid regurgitation had the classic triad of physical signs indicative of tricuspid regurgitation.

A spectrum of echocardiographic abnormalities was noted in patients with tricuspid valve endocarditis. M-mode and cross-sectional echocardiography, in conjunction with echocardiographic saline contrast studies, should prove valuable in the diagnosis and serial follow-up of such patients. The technique is useful in detecting complications such as chordal rupture and tricuspid regurgitation.

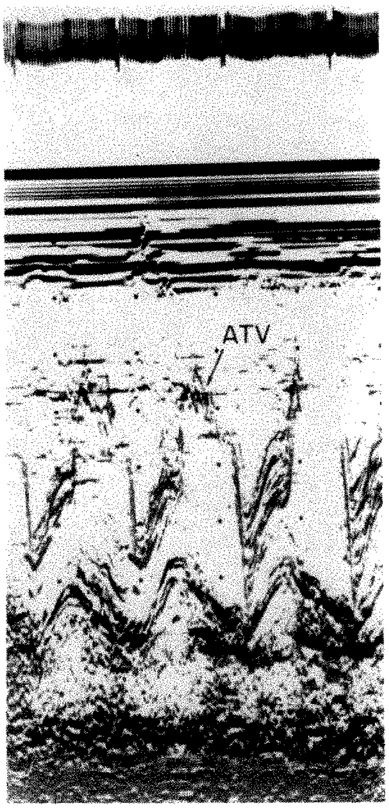

Fig. 7 *Echogram of the tricuspid valve in a patient with endocarditis, which demonstrates irregular fluttering of the anterior tricuspid leaflet (ATV) indicative of ruptured chordae tendineae.*

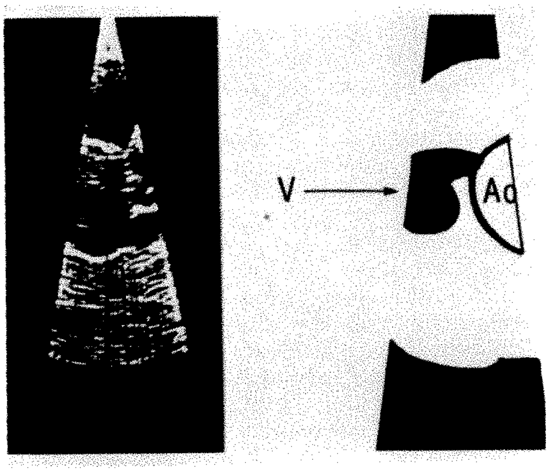

Fig. 8 *Cross-sectional echocardiogram in the short axis view, illustrating a large mass (V) on the tricuspid valve consistent with a vegetation. Ao, aortic root.*

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Long-term results of pulmonary autograft for aortic valve replacement

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SUMMARY Eighty-five survivors who left hospital after pulmonary autograft replacement for severe aortic regurgitation have been followed critically. Five patients died in the first five years and 80 were followed for six to 11 years. Important aortic regurgitation occurred only early and was always related to technical malpositioning of one autograft cusp. Seven patients with fascial pulmonary valves had problems, requiring removal in four. There was a small (2%) morbidity from the right sided homograft and six were removed five to seven years later for progressive calcification; three of these had been irradiated. Despite a high incidence of trivial diastolic murmurs this valve replacement is still preferred for young patients without dilated aortic roots since the survivors remain well, with excellent, maintained relief of outflow obstruction, without problems from haemolysis and thromboembolism, and without deteriorating autograft function or need for anticoagulants. Histology of five autografts examined up to seven years after operation has shown normal living architecture.

The use of biological valves for aortic valve replacement has been well established (Ross, 1962; Barratt-Boyes, 1964; Barratt-Boyes *et al.*, 1969) and in many ways they have been shown to be superior to prosthetic valves particularly when long-term anticoagulant therapy is undesirable. The longest experience has been with the cadaveric aortic homograft but even with better techniques of sterilisation there have been occasional problems with degeneration and infection. An alternative and theoretically ideal valve replacement is the patient's own pulmonary valve (pulmonary autograft) (Ross, 1967). Indeed, of the few pulmonary autografts removed or retrieved at necoropsy, pathological examination has shown that the pulmonary autograft contains living cells and normal valvular architecture up to 7 years after the operation (L. Becu, personal observations). This suggests that this valve may retain the potential for good function for a longer period then other available valve substitutes. With 11 years of experience and improved techniques it is appropriate to report the late results of 85 patients who left hospital after aortic valve replacement with a pulmonary autograft.

Subjects and methods

Between July 1967 and July 1972 (Fig. 1), 85 consecutive patients having had their aortic valve

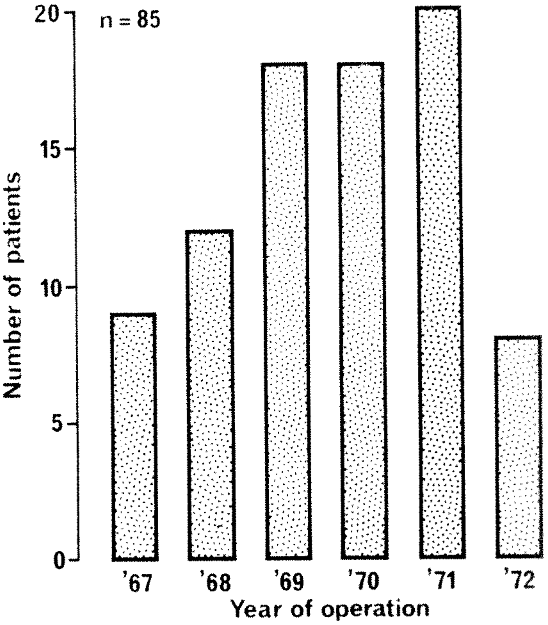

Fig. 1 *Year of operation of 85 survivors of pulmonary autograft.*

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[2] Research Secretary initially supported by a one-year grant from the British Heart Foundation and subsequently by an anonymous donor.

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replaced with their own pulmonary valve left the National Heart Hospital after one month and have been regularly assessed since. The surgical technique with cardiopulmonary bypass at normothermic temperatures consisted of excision of the patient's own normal pulmonary valve which was then used to replace the excised diseased aortic valve (Ross, 1967; Gonzalez-Lavin *et al.*, 1970). A homograft was used to reconstruct the right outflow in 77 and autologous fascia lata in eight in 1968 and 1969.

The age of patients was 12 to 54 years (mean age 33 years), with 59 (69%) below 40 years. Of the 85 patients, 26 had severe aortic regurgitation or mixed aortic valve disease with dilatation of the aortic root. This technique was not used in patients with Marfan's disease, dissection of the aorta, and other diseases causing unusual aortic root enlargement. No patient had active infective endocarditis at the time of operation.

Previous aortic valve surgery had been performed two to seven years earlier in 14. At the same time, 11 patients had other lesions corrected, such as closure of ventricular septal defect, subvalvar myotomy, and mitral valvotomy.

Clinical assessment, which was made every six months included physical examination, 12 lead electrocardiograms, routine penetrated posteroanterior and lateral chest radiographs for detection of graft calcification, and phonocardiography. Fifty-four (63%) had cardiac catheterisation with measurement of gradients across the right and left ventricular outflows, aortography, and pulmonary arteriography when possible

Results

Five patients died in the first five years, and 80 have been followed for six to 11 years.

LATE MORTALITY

There have been 11 (13%) late deaths (Tables 1A and 1B). In six (7%) death was directly related to problems with either the autograft or the right sided reconstruction; in five there were other causes.

After five postoperative years, 78 of the original 85 were alive. Of 18 possible survivors, 14 were alive after eight years and no deaths have occurred after the eighth postoperative year.

SEVERE AUTOGRAFT REGURGITATION (AORTIC REGURGITATION)

Important autograft regurgitation, as judged by the presence of a loud immediate diastolic murmur, widening of the pulse pressure above 50 mmHg with a diastolic pressure lower than 70 mmHg at rest, appeared during the first year in five (Fig. 2A and 7). One had been discharged with a clinically competent autograft two weeks after operation and

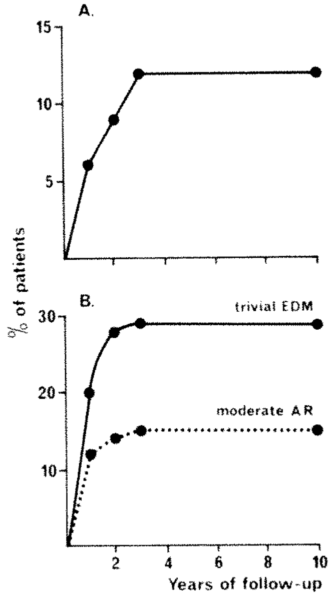

Fig. 2 *(A) Incidence and time of appearance of important autograft (aortic) regurgitation in surviving patients after pulmonary autograft. (B) Incidence and time of appearance of early diastolic murmurs in those surviving patients who did not develop severe autograft regurgitation. For both graphs, on the vertical axis: percentage of surviving patients; on the horizontal axis: postoperative years.*

Table 1A *Cause of death in six patients in whom death was related to a problem with either the homograft or the autograft valve*

Case no.	*Age (y)*	*Postop year*	*Cause of death*	*Findings at necropsy*
1	15	1st (2/12)	Severe autograft regurgitation	Malposition of one of autograft cusps
2	26	1st (9/12)	Pulmonary embolism after replacement of infected homograft (fungal)	No necropsy
3	34	1st (10/12)	Severe autograft regurgitation	No necropsy
4	40	3rd	Severe fascia lata valve obstruction	No necropsy
5	49	6th	Early death after reoperation for mitral valve disease, autograft regurgitation, and homograft stenosis	Autograft had a perforated cusp; homograft severely calcified and degenerated
6	32	7th	During reoperation for autograft root sclerosis	No necropsy

Table 1B *Cause of death in five patients in whom death was not related to either of the valves*

Case no.	*Age (y)*	*Postop year*	*Cause of death*	*Findings at necropsy*
1	41	4th	Coronary heart disease; previous infarction + left ventricular aneurysm	No necropsy
2	54	6th	Coronary heart disease	No necropsy
3	33	6th	Sudden death	Autograft and homograft in perfect condition
4	42	6th	Myocardial infarction	Signs of very recent subendocardial infarction; autograft and homograft in perfect condition
5	50	7th	Sudden death	Autograft and homograft in perfect condition

returned a month later with acute severe aortic regurgitation, requiring immediate reoperation which showed that the cusps had torn away from the frame; this was the only frame mounted autograft in the series.

By the end of the third postoperative year, 10 (12%) had important autograft regurgitation but the incidence has not increased since (Fig. 2A). Of these 10 patients, nine have required reoperation; in four the valve was repaired or repositioned and in five it was replaced. The remaining one with torrential regurgitation refused surgery and is alive nine years later leading a sedentary life.

INCIDENCE OF DIASTOLIC MURMURS

Excluding the 10 with serious autograft regurgitation, immediate diastolic murmurs were noted in 38 patients (44%) in the first three postoperative years (Fig. 2B). In 13 (15%) where there was some pulse alteration or aortic regurgitation was shown by angiography, the murmur was obviously caused by mild to moderate aortic regurgitation. In 25 (29%), the faint murmur was not associated with other signs and it was uncertain clinically whether it was the result of pulmonary or aortic regurgitation unless investigation had designated the origin (Fig. 2B). In 27, these murmurs appeared in the first year, eight more developed murmurs in the second year, and the rest in the third (see Fig. 6). There has been no increase in the incidence of diastolic murmurs after the third year. All the patients in this group are asymptomatic and not requiring treatment.

PROBLEMS RELATED TO PULMONARY VALVE REPLACEMENT

In the eight patients who had their right ventricular outflow tracts reconstructed with fascia lata the results were obviously unsatisfactory (Ross and Somerville, 1971) (Fig. 3). Of these patients, four have already had their valves replaced and one is awaiting reoperation for severe right outflow tract obstruction. Another patient had a pulmonary embolism after an episode of infective endocarditis and, since he had no autograft regurgitation and there was no systemic emboli during his illness, it was assumed that the infection took place on the already stenosed fascial valve. One patient died while awaiting surgery for significant stenosis and regurgitation of his valve. Only one patient with a fascial pulmonary valve is well and without any problems. In all patients reoperated on, the fascial cusps were completely fused and reduced to a thick narrow fibrous ring.

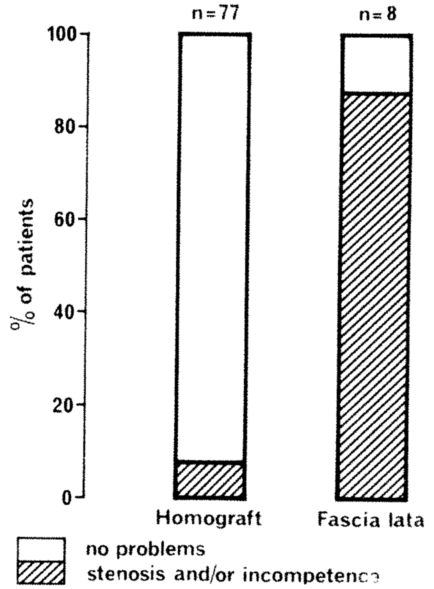

Fig. 3 *Incidence of postoperative right-sided problems in relation to the right ventricular outflow tract reconstruction in 85 patients who had aortic valve replacement with a pulmonary autograft. There were a large number of problems with right-sided valves in the eight with fascial reconstruction.*

When aortic homografts have been inserted in the pulmonary position, sterilised by physicochemical methods up to 1969 and thereafter with antibiotic solutions (Longmore *et al.*, 1966; Yacoub and Kittle, 1970; Lockey *et al.*, 1972; Al-Janabi and Ross, 1973), the incidence of complications has been low (Fig. 3). Two had early problems requiring reoperation (Table 2); one developed fungal endocarditis and died during reoperation and the other was saved after the rupture of an infected right

Table 2 *Summary of reasons for reoperation, state of valves, and outcome of patients who required reoperation*

Case no.	*Postop year*	*Reason*	*Surgery*	*Autograft state*	*Right-sided valve state*	*Homograft sterilising method*	*Outcome*
1	1st	Ac AR	A by Starr	Cusp rupt			A and W
2	1st	H inf	H by H		Inf	Eth ox FD	A and W
3	1st	H inf	H by H		Fungal	Fr AB	Died early postop
4	2nd	AR	A by FL	Prol cusp			A and W
5	2nd	FL sten	FL by H		FL sten		A and W
6	3rd	AR (post inf end)	A by H	Prol cusp			A and W
7	3rd	FL sten	FL by H		FL sten		A and W
8	5th	AR, FL sten	A by Björk, FL (Dacron)	Det cusp	FL sten		A and W
9	6th	MVD, AR, H sten	M by Starr, A by Starr, H by H	Perf cusp	Calc	Eth Ox, irrad FD	Died early postop
10	6th	FL sten, AR	FL by H, A rep	Perf cusp	FL sten		A and W
11	7th	AR, H sten	A by Starr, H by H	Prol cusp	Calc	Eth ox FD	A and W
12	7th	A root sclerosis	A by Björk	Woody, inflamm			Died early postop
13	7th	AR	A rep	Prol cusp			A and W
14	8th	MR, HR. AR	M by dura, H rep, A rep	Prol cusp	Calc	Irrad FD	A and W
15	9th	HR	H rep		Calc	Eth ox FD	A and W
16	10th	HR + sten	H by xeno		Det cusp calc	Irrad FD	A and W
17	10th	AR, HR, MVD	A rep, H rep, M by Xeno	Prol cusp	Cusps thickened	Eth ox FD	Still has imp AR

A, autograft; AB, antibiotic; Ac, acute; A and W, alive and well; Calc, calcified; Det, detached; Dura, dura mater valve; End endocarditis; Eth ox, ethylene oxide; FD, freeze dried; FL, fascia lata valve; Fr, fresh; H, homograft; Imp, important; Inf, infected; Inflamm, inflammatory; Irrad, irradiated; M, mitral valve; MVD, mitral valve disease; Perf, perforated; Postop, postoperatively; Prol, prolapsed; R, regurgitation; Rep, repaired; Rupt, ruptured; Sten, stenosis; Xeno, xenograft.

ventricular aneurysm at the proximal end of the graft. He has survived 10 years, well, without autograft regurgitation and living a normal life in one of Her Majesty's prisons where he is confined for robbery with violence.

A further six patients required reoperation for homograft dysfunction. Calcification and rigidity of the cusps was found in five and one cusp was detached from the calcified wall in one. Three of these homografts were replaced and three were able to be repaired using a unicusp homograft. They had been sterilised by ethylene oxide and freeze dried in three, irradiation and freeze dried in two, and by the combination of both methods in the remaining one.

Calcification of the right sided homografts was radiologically detected in 22 patients (28%) but it was not evident before the second postoperative year (Saravalli *et al.*, 1979) and not associated with haemodynamic problems in 16.

REOPERATIONS

Seventeen patients have had reoperation one to 10 years after the original surgery (Table 2). Seven (41%) were reoperated on in the first three years and 10 in the remaining years of follow-up. Five patients were reoperated on for isolated autograft regurgitation, six for problems related to the pulmonary valve replacement, and a further six for the combination of right and left sided problems (Table 2). The original autograft has had to be removed in seven patients, of whom five are still surviving with another valve (see Fig. 6). In most of these cases, the histological study of the autograft has persistently showed a striking conservation of the valvular tissue up to seven years after implantation. Elastic layers were shown to be preserved and normally arranged and large amounts of living cells were present among them (Fig. 4). There has been no sign of calcification or endocardial or medial thickening. This remarkable histology was also found when autografts from necrospy specimens could be examined. The only exception to this has been one case in which a woody inflammatory process had taken place in the autograft root, involving its cusps, in a patient who had infective endocarditis three months after the original operation.

REINVESTIGATION

There has been no established policy regarding reinvestigation in view of the difficulties of getting patients from long distances back into hospital. However, 54 (63%) out of the 85 reported patients have had haemodynamic studies three weeks to eight years after operation. Twenty-nine were catheterised during the first postoperative year, 22 as a routine test to assess surgical results, and seven because of the appearance of complications or evaluation of residual lesions. Thirteen patients had a second postoperative catheterisation eight months to eight years after the first one. This was performed in 12 cases because of changes in the clinical state.

All investigations included measurement of gradients across the right and left ventricular outflow, right and left ventricular angiography, aortography, and pulmonary artery arteriography.

In no case was a pulmonary autograft gradient

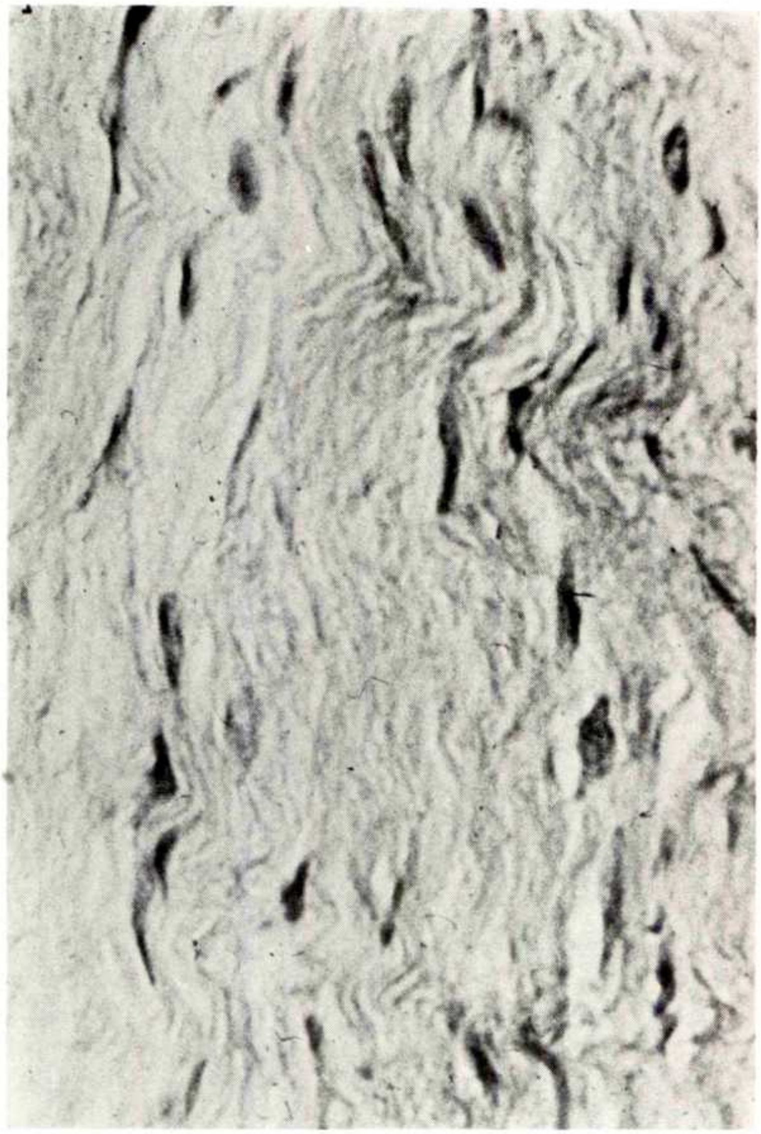

Fig. 4 *Masson's trichrome stain (original magnification ×40). Section of autograft cusp seven years after operation. There are a large number of living cells among the orderly arrangement of a collagenous matrix which contains a sparse but well-formed background of elastin.*

higher than 12 mmHg found. A trivial degree of autograft regurgitation was assessed in 35 asymptomatic patients. However, the degree of regurgitation found at the first investigation had not increased in the 13 patients who underwent a second study. In all patients who have not shown signs of important regurgitation because of graft malposition, routine aortography showed normal looking aortic root with normal opening and closing of pliable autograft cusps.

Fascia lata valves used for right sided reconstruction have always shown important gradients at reinvestigation whereas gradients of only up to 23 mmHg have been recorded across the right sided homografts at first postoperative catheterisation. These gradients increased significantly at the second investigation in eight patients, six of whom have already had homograft replacement or repair for homograft calcification and obstruction (Table 2). A properly functioning homograft is shown (Fig. 5).

OTHER PROBLEMS

Seven patients have had the certain clinical diagnosis of infective endocarditis one month to seven years after surgery. In two cases this produced serious autograft regurgitation which led to autograft replacement while in one case a woody inflammatory

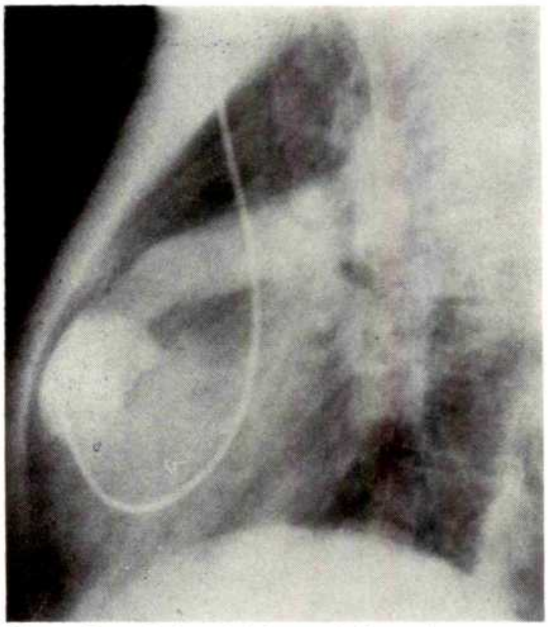

Fig. 5 *Lateral view of right ventricular angiogram from a patient who had pulmonary autograft and homograft replacement of the pulmonary valve six years before. Cusps and outflow appear normal without any systolic gradient.*

process involving the whole aortic root with subsequent involvement of the autograft cusps developed, causing severe regurgitation which also necessitated reoperation. In the remaining four cases, after treatment of the illness, significant clinical changes did not appear. Of these seven patients, two had already had infective endocarditis before surgery.

One patient has been living for seven years with a pacemaker because of complete heart block dating from the time of surgery and three others are neurologically handicapped after perioperative complications; these problems were seen only among the first 12 patients in the series.

Two patients have required operation for peripheral vascular disease and a further two have developed important mitral valve disease and await reoperation for this. Five patients developed systemic hypertension which has been controlled by medical therapy and has not been the cause of increasing autograft regurgitation or deterioration.

GENERAL CLINICAL STATE

Sixty-nine surviving patients are living with the same original autograft six to 11 years after operation while five others are surviving with another valve in the aortic position. Fifty-six patients are asymptomatic, physically and mentally, and are able to do full time jobs. Twelve of these patients are doing strenuous work, five others regularly play sport, and a further two are attending college. There have also been six successful pregnancies and deliveries in four female patients, three to six years after operation.

Discussion

A superficial look at the late results of pulmonary autograft may suggest to the unwary critic that perhaps there are too many problems with this complex operation for aortic valve replacement. However, this series includes all patients since the technique was introduced and so the early mortality and some of the late results are influenced by the errors of pioneering. Thus, it is unreasonable to compare the late results of the first 50 survivors of this procedure with some other form of aortic valve

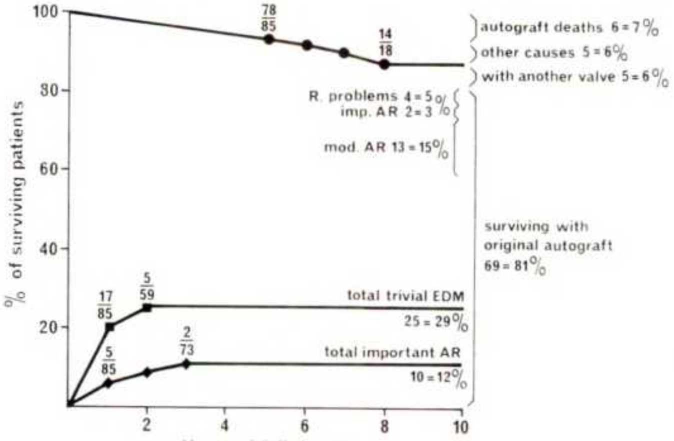

Fig. 6 *Summary of current state and problems in 85 patients who left hospital after pulmonary autograft. Lower numbers relate to actual total of patients who had survived that length of time and upper numbers relate to those with the complication.*

replacement with the 'trial and error' excluded. Unquestionably the learning period of surgical technique included errors which can now be avoided since the related problems are no longer seen in the recent series. For instance, in the first 20 patients, no coronary perfusion or real myocardial protection was used, sometimes leading to fatal circumferential subendocardial infarction; furthermore in the survivors of this period, there may well have been myocardial damage and scars to account for repetitive ventricular tachycardia in three fatal cases. In all three the autograft valves were perfect and living. Furthermore, operative damage to conducting tissue with production of right bundle-branch block (four) and complete heart block in two occurred early on and obviously contributed to some morbidity.

To evaluate a valve used for replacement of a diseased valve, attention must be primarily directed to the function and degeneration of that valve. With regard to the autograft, a few important facts emerge. Cusp rupture has occurred only once in an 11-year period in the only frame mounted autograft used for technical reasons in a boy who already had two previous aortic valve operations. Important aortic regurgitation occurred early and did not develop in any after the first three years. In those with this problem who were reoperated or who died the aortic regurgitation has always been the result of malposition of one cusp which obviously causes important regurgitation in a manner which predisposes to progression. This is a technical problem related to positioning and tailoring of the root. It occurred mostly in patients with preoperative dominant or lone aortic regurgitation (60%) so that the technique is rarely used in such patients with pronounced dilatation of the aortic root which cannot readily or safely be reduced. The microscopical features of the autograft show normal histology with aligned living cells looking like those of a normal valve. No calification or dead tissue has been found in any. Indeed, one of the major theoretical and practical attractions is that it remains living and generally free of disease. One exception to this is a 23-year-old woman with rheumatic valves who had a serious febrile illness three months after autograft replacement of her regurgitant aortic valve. Aortic regurgitation progressed and seven years later the valve was replaced. Whether the woody inflammatory tissue in the root and the base of the cusps was an autoimmune process or a chronic valvulitis we do not know. The purpose of mentioning this exception is to document it so that others may find a solution.

The relatively high incidence of immediate diastolic murmurs with little or no haemodynamic change has not been a cause for concern. They appeared only in the first three years without progression or increasing incidence thereafter. We suspect that the majority are a result of trivial aortic regurgitation. In some where aortography has confirmed a competent aortic valve, the murmurs clearly originated from the right side. The critics of this procedure understandably comment on this high incidence of trivial murmurs but this is not a reason for alarm since the haemodynamic lesion appears to be static in the first decade, there is no reason to attribute it to tissue degeneration, and the long-term prognosis of trivial rheumatic or congenital aortic regurgitation is excellent. Indeed, the prognosis of autograft regurgitation may be even better since the valve seems not to be prone to calcification, thickening, or rupture. The incidence of late infective endocarditis on the autograft is only 6 per cent, less than in homografts or mechanical valves, but shows that these patients must be protected for life.

The real problem which worries us still is the replacement for the removed pulmonary valve. It is irrelevant to the main theme to discuss the now known disaster of using fascia lata (Ross and Somerville, 1971). This unquestionably added to the late incidence of reoperation and often precipitated reinspection or surgery on the autograft. When surveying the problems of the well-tried homograft in the right ventricular outflow tract there was an acceptable low early morbidity (2%) from infection, clearly related to methods of sterilisation which are common to the use of homografts in any site, varying from centre to centre and remaining partly unsolved. However, six patients (7%) after the sixth postoperative year required removal of the right-sided homograft valve for progressive symptomatic obstruction and/or regurgitation. Strangely, this has not been the experience using the same homografts for repair in congenital cyanotic heart disease (Somerville, 1975) where the graft-bearing wall calcifies earlier and more intensely (Saravalli *et al.*, 1979).

Three of the six valves had been irradiated before surgery which may have led to the degenerative problems. However, in one, not irradiated, we have no obvious explanation for dysfunction. Whether it relates to the unknown details of the age and sex of the donor or to technical problems of malpositioning the graft cannot be stated. Unquestionably the details of the donor of the homograft must be documented as they may influence the fate of homograft valves in all sites.

The clinical state reflects accurately the function of the homograft 'pulmonary' valve and the autograft aortic valve. There were no surprises and with the exception of the above-mentioned problem there was no progressive change in serial studies. The autograft aortic valve invariably looks surprisingly normal and relief of left outflow obstruction is satisfactory, resting gradients being 0–12 mmHg.

It is accepted that this is a technically more difficult, demanding, and time-consuming operation than others used for aortic valve replacement and as such must carry a higher initial mortality. However dexterous the surgeon, the procedure may not be possible in many centres because of lack of homografts, funds, or excess numbers of patients.

In eight young patients referred specifically for pulmonary autograft, it could not be undertaken because of minor congenital abnormalities in the pulmonary valve.

In favour of the procedure is that we have shown that the normal pulmonary valve can function normally for a decade and in those few examined histologically, it retains the features of 'living' tissue. The technical problems are mainly solved and we believe from our studies that this is the operation of choice in young patients with good left ventricular function, a normal pulmonary valve, and no aortic root dilatation or autoimmune disease.

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Comparative method for actuarial analysis of cardiac valve replacements

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SUMMARY The use of survival analysis in cardiac surgical reports has been widely accepted in order to characterise and compare performances of different valve prostheses. However, the analyses that have been described elsewhere may be improved in several respects. The original method proposed for prosthetic valve evaluation examined follow-up related to patients rather than the valves themselves and therefore neglected the possibility of factors other than the valve itself which could affect the fate of cardiac patients. Furthermore, there has not yet been any application of life table methods to compare two different sets of data, or to estimate the average time before an event occurs.

The present work defines valve function and malfunction and separates patient survival from valve performance. We define statistical indices, namely the median remaining lifetime and the instantaneous decrement rate. Both indices can be useful; the former measures the average survival time and the latter focuses attention on the intensity of risk changes. Using established statistical theory we calculate the significance level of difference between two independent survival rates. We qualify the presentation of probabilities with a statement of the associated standard errors.

Statistical analysis based on the life table has been proposed as an objective method for the evaluation of long-term results in cardiac surgery (Anderson *et al.*, 1974; Grunkemeier *et al.*, 1975). This method offers an accurate and simple means for estimating the prognosis of patients with chronic disease. The method has been used for many years to determine survival rates of cancer victims. Several authors have provided comprehensive descriptions (Berkson and Gage, 1950; Merrell and Shulman, 1955; Cutler and Ederer, 1958; Axtell, 1963). The approach was called the 'actuarial method' by Berkson and Gage (1950) who used a formula first proposed by Frost (1933), recognising that it had been widely used by actuaries since the 19th century as an application of the theory of 'multiple decrements' (Benjamin and Haycocks, 1970). Consideration of these problems first started with Daniel Bernoulli's discussion of the smallpox inoculation problem which is reviewed by Karn (1931).

Calculation of patient survival

We shall consider the application of actuarial analysis to follow-up studies where the population under investigation has undergone a valve operation. We shall define patient survival and valve performance to be separate entities. Firstly, we shall discuss the method for assessing patient survival, and then extend the results, in a later section, to assessing valve performance.

In measuring the proportion of patients alive n years (say, n = 5) after the operation, an important advantage of the actuarial method is that it uses all the information collected up to the time of analysis (that is the closing date of the study). Thus, one need not restrict one's attention to only those persons whose operation occurred more than five years before the closing date. Those entering four, three, two, and one year earlier contribute much relevant information to the evaluation of the probability of surviving five years. This extra information is utilised by pooling the data from groups of patients entering the study at different times.

The increased precision in estimating survival probabilities has been documented (Merrell and Shulman, 1955; Cutler and Ederer, 1958). This advantage is particularly relevant to surgical studies where the bulk of experience is concentrated at the earliest durations though the surgeon may be particularly interested in results at the longest duration after the operation.

At the closing date of such a follow-up study, patients are likely to have been observed for varying

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lengths of time, some having had the operation a long time previously, others more recently. Some patients will have died, the time of death being usually known accurately (with other end points, for example the occurrence of valve complications, the precise time of the event may not be known). Other patients are known to be alive, and would have survived further had the study been extended. Some may have been lost to follow-up for various reasons between successive examinations. Others may have been removed from the study for medical reasons (perhaps by the intervention of another disease or death from a different cause).

These last three groups, viz. (a) those who would have continued had not the closing date of the study intervened; (b) those who have been lost to follow-up; and (c) those who have been removed from the study, create a common category called 'withdrawals'. The combined group is of prime importance since it is usually part of the data, and it is this which makes the actuarial method of probability calculation necessary. If there were no withdrawals and each patient was observed until their time of death, the calculation of survival probabilities at different times after operation would be simple. Thus, the n year probability of surviving would be the same as the proportion of patients with survival times greater than n. The problems would be reduced to ascertaining the distribution of survival times.

The mathematics of the actuarial method are not very difficult but it is not necessary for clinicians to understand the theory which is well established. This is set out in Appendix I.

Previous cardiac surgical reports which have discussed the use of the actuarial method have not considered the problem of comparing two sets of survival data. We present in Appendix I a method for testing how statistically significant is the difference between two independent sets of data.

In addition we introduce the instantaneous probability of dying which characterises the change in the intensity of risk, and is very useful for drawing attention to points where there is a dramatic change in experience. We also introduce the median remaining life-time which measures the average survival time.

These techniques are described in detail in Appendix I in terms of patient survival. However, they may also be used for measuring valve performance, and will be mentioned in the following sections.

Calculation of valve performance

When introducing the actuarial method to cardiac surgery, Anderson *et al.* (1974) proposed the assessment of patient survival after the insertion of a given prosthetic valve. They assumed that postoperative survival and/or complication-free survival was predetermined by the quality of the given valve prosthesis. Though such an assumption is reasonable when the main risk factor during the whole follow-up period is the valve, it neglects the possibility of an excellent prosthesis when the fate of patients will be determined by factors other than the prosthesis itself. Moreover, the method of constructing the life tables for cardiac surgical patients has been designed to assess follow-up not on a condition, such as a valve, but on the carrier of that condition, the patient. Thus, the straightforward interpretation of data on patient follow-up as a characteristic of valve performance can be misleading. Nevertheless, patient survival and valve performance can be separated, and given independent consideration.

The risk attributed to biological, prosthetic, or bioprosthetic cardiac valves is caused by one or more of five main malfunction categories as follows:

(1) Mechanical malfunction. Stenosis and/or regurgitation, as defined in the NYHA definition of cardiac anomalies, and irrespective of the pathomorphology of stenosis and regurgitation involving paravalvar leaks, or a haemodynamically significant gradient across an otherwise well-functioning prosthetic or bioprosthetic valve.
(2) Infection. Involvement of the valve in septic conditions, described as acute or subacute endocarditis by the NYHA definition.
(3) Thrombotic apposition on valve surface with or without consecutive embolism. Embolism in the relevant side of the circulation with or without thrombotic apposition on the valve.
(4) Pathological bleeding caused by anticoagulation resulting from prosthetic valve.
(5) Haemolysis. Clinically manifest haemolysis in the presence of a given valve and without coexisting haematological disease.

In terms of actuarial analysis any valve can be *free of fatal malfunction,* that is the patient is either alive or dead and the *death is neither caused by nor accompanied by any of the above mentioned five conditions.* Next, the valve can be functioning until the *cessation of function,* which means either until a valve-related death or the removal of the valve and its replacement by another cardiac prosthesis. Finally the valve can *function without complications* corresponding to the criterion that none of the above mentioned five conditions has yet occurred (Fig. 1).

Thus, the meaning of complication is both cumulative and comprehensive involving all of the possible malfunctions attributed to the given valve.

Actuarial analysis can be adapted to the analysis

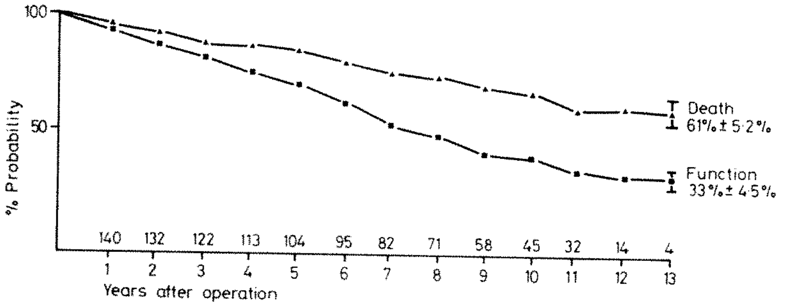

Fig. 1 *Freeze dried homograft valves. Probability of valve related death and valve function without complication (cumulative).*

of non-fatal events (for example, complications), by considering such events as terminal, that is by treating the experience which individuals or valves contribute to the study, in the same way as death is treated in Appendix I.

When assessing valve performance, the withdrawal category will comprise the following three groups of valves, viz.

(a) Those which would have continued had not the closing date of the study intervened.

(b) Those which have been lost to follow-up.

(c) Those who die and the cause is either *not* related to the valve or is unknown.

The life tables for assessing valve performance are constructed in an analogous way to that described in Appendix I for patients and in Appendix II we present a worked example. For convenience, in the definitions below, we use terms like 'death' or 'loss' to refer to valves, even though it is the patient who dies or who is lost.

Consider the interval between x and x+1 years after the operation.

Let L_x be the number of originally inserted valves functioning at the beginning of the interval.

Let D_x be the number of deaths, caused by or accompanied by any of the above five malfunctions, occurring in the interval.

Let W_x be the number of valves withdrawn during the interval.

Let R_x be the number of valves removed at successful re-operation during the interval.

Let C_x be the number of valve complications involving neither death nor reoperation during the interval.

Then $L_{x+1} = L_x - (D_x + W_x + R_x + C_x)$ and a life table may be constructed.

Three different survival curves will be derived relating to free of fatal malfunction, free of malfunction, and free of complication. These will be considered in turn.

FREE OF FATAL MALFUNCTION

Let $E_x{}^d$ be the number of valves exposed to the risk of death caused or accompanied by any of the five malfunctions during the interval.

Then $E_x{}^d$ is not equivalent to L_x since the withdrawals, removals, and complications who have not completed the interval of observation under consideration must not be credited with having done so. In order to reach an expression for $E_x{}^d$, we shall assume that these valves withdrawing (W_x), reoperated (R_x), or experiencing complications (C_x) in the interval x to x+1 are exposed to the risk of dying from a valve related cause for half the interval, so that

$E_x{}^d = L_x - \frac{1}{2}(W_x + R_x + C_x)$.

The actuarial estimate of the probability of a valve related death in the interval x to x+1 for a valve alive and functioning at x is $q_x{}^d$ where

$$q_x{}^d = \frac{D_x}{E_x{}^d}$$

Given $q_x{}^d$, formulae may be set up, as in Appendix I, for $P_x{}^d$, cumulative probability of surviving free of a valve related death from o to x; $\mu_{x+\frac{1}{2}}{}^d$, the instantaneous valve related death rate at $x+\frac{1}{2}$; $m_x{}^d$, the median remaining lifetime for a valve free of fatal malfunction at time x after operation; and the corresponding standard errors.

These functions are estimates of the values that would have been obtained if the valve removals, complications, and withdrawals were eliminated as types of departure from the study.

FREE OF MALFUNCTION

Let $E_x{}^{dr}$ be the number of valves exposed to the risk of malfunction during the interval x to x+1.

Then, after a similar argument to the above with corresponding assumptions, one can show that $E_x{}^{dr} = L_x - \frac{1}{2}(W_x + C_x) = E_x{}^d + \frac{1}{2}R_x$.

Then the actuarial estimate of the probability of a malfunction occurring in the interval x to x+1 for a valve alive and functioning at x is $q_x{}^{dr}$ where

$$q_x{}^{dr} = \frac{D_x + R_x}{E_x{}^{dr}}$$

Given $q_x{}^{dr}$, formulae may be set up, as above, for $P_x{}^{dr}$, the cumulative probability of surviving free of a malfunction from o to x; $\mu_{x+\frac{1}{2}}{}^{dr}$, the instantaneous malfunction rate at time $x+\frac{1}{2}$; $m_x{}^{dr}$, the median lifetime remaining for a valve free of a malfunction at time x after operation; and the corresponding standard errors.

FREE OF COMPLICATION

Let $E_x{}^{drc}$ be the number of valves exposed to the risk of complication during the interval x to x+1. Then, after a similar argument to the above with corresponding assumptions, one can show that $E_x{}^{drc}=L_x-\frac{1}{2}W_x=E_x{}^{dr}+\frac{1}{2}C_x$.

Then the actuarial estimate of the probability of a complication occurring in the interval x to x+1 for a valve alive and functioning at x is $q_x{}^{drc}$ where

$$q_x{}^{drc}=\frac{D_x+R_x+C_x}{E^{drc}}$$

Given $q_x{}^{drc}$, formulae may be set up, as above, for $P_x{}^{drc}$, the cumulative probability of surviving free of a complication from o to x; $\mu^{drc}{}_{x+\frac{1}{2}}$, the instantaneous complication rate at time $x+\frac{1}{2}$; $m_x{}^{drc}$, the median remaining lifetime for a valve free of complication at time x after operation, and the corresponding standard errors.

INDIVIDUAL AND CUMULATIVE EVENT-FREE CURVES

The quality of life may be analysed by the actuarial method considering not only death but also possible complications, as described above. Two fundamentally different methods have been proposed by the Oregon University Group: the individual complication-free survival curve (Anderson *et al.*, 1974), for example P^d, P^r, P^c, and the cumulative complication-free survival curve (Grunkemeier *et al.*, 1975), for example P^{dr}, P^{drc}.

The term 'cumulative' is thus used in two senses. Firstly it is used to refer to the combining of complications (or, in general, decrements) and secondly it is used to refer to the combining of successive years after the operation. This dual use of the same word is confusing. We suggest a more suitable nomenclature would be use of the term 'multiple complication' (and, in general, 'multiple decrement'), for the first purpose, and to use 'cumulative' for the second purpose only. So individual event-free curves could be described as 'single decrement'.

The individual event-free calculation (that is single decrement) analyses only one selected complication and assumes that no other complication can occur, not even death of the patient. Calculating each individual event-free complication curve (for example, embolism, endocarditis) will involve the death being included in the withdrawn category (as above) and thus contributing a half-year event-free survival.

Because of this disadvantage, Grunkemeier *et al.* proposed the cumulative event-free survival curve (multiple decrement) which considers death or complication as a final event, whichever occurs first. Not only one, but two, three, or all the possible complications can be analysed in this way. Whichever occurs first, death or any of the complications will count as a final, terminating event, and the rest of the patients will experience an event-free survival.

The reasonable difference between the two methods can be well illustrated on the follow-up of patients, or, as in this case, on valve performance (see Appendix II). This is based on 140 isolated aortic valve replacements between 1964 and 1967 at the National Heart Hospital. There was not a single embolism, 87 per cent of the valves were free of technical failure, 83 per cent free of infective disease, and 51 per cent free of degenerative failure after 13 years.

Not surprisingly, the cumulative event-free survival curve (multiple decrement) creates another impression. There are only 33 per cent of the valves functioning free of complication. In fact, the freeze drying of the homografts was abandoned well before actuarial analysis could have come into effect. Obviously, the conclusion can be drawn that fair, independent judgement on a valve and on its overall performance can scarcely be made without considering the cumulative complication-free survival curve (multiple decrement).

None the less, the individual event-free curves (single decrement) can be very useful for the ex-expression of the composition of complications as well as their relation to each other. In this way it becomes easy to show that technical failures cause an early cessation in valve performance, that infection has not been recorded after the first 10 years, and that degeneration begins later but rises steadily.

Certainly, in this case the comment would be 33 per cent event-free valve function after 13 years, with some early technical failure, later a continuing degeneration as well as some infection causing malfunction.

The danger of considering individual event-free curves (single decrement) in assessment of patient survival or valve performance is increased when there is no single major risk factor, but the complications are caused by several lesser ones. The danger increases in proportion to the number of complication-groups taken into account. Ten individual complications each with a 90 per cent complication-free survival can easily mean that neither a single patient nor valve survives without complication. Thus, the cumulative event-free survival function (multiple decrement) should be the primary approach to an actuarial analysis in the assessment of valve performance.

RELATION BETWEEN SURVIVAL CURVES

If the above arguments had been used to derive estimates of the probability of the occurrence of a valve removal $q_x{}^r$ or the probability of the occurrence of a non-fatal complication involving no removal $q_x{}^c$, we could construct a free of removal survival curve $P_x{}^r$ and a free of non-fatal complication survival curve $P_x{}^c$. Then it may be shown that (Benjamin and Haycocks, 1970): (a) the instantaneous probability of a complication occurring is equal to the sum of the three single decrement instantaneous probabilities, that is

$$\mu^{drc} = \mu^d + \mu^r + \mu^c$$

and (b) the probability of surviving without a complication is equal to the product of the three single decrement probabilities of surviving, that is

$$P^{drc} = P^d \,.\, P^r \,.\, P^c.$$

Thus the instantaneous probabilities combine together in an additive way, and the survival curves combine together in a multiplicative way.

Because of this multiplicative property, it may be shown that the difference between two survival curves has a simple interpretation (Grunkemeier *et al.*, 1975). For example, the difference $P_x{}^d - P_x{}^{dr}$ (between the survival curve free of valve-related deaths and the survival curve free of malfunction) represents the probability of a patient being alive at time x but with a valve replaced. However, no information is provided about the subsequent experience of such patients with replaced valves.

In actuarial mathematics, functions like P^r, P^d, and P^c are called single decrement functions, and those like P^{rd} and P^{rcd} are called multiple decrement functions. Thus, these two factors must be given separate assessments to achieve unbiased statistical analysis.

We acknowledge the invaluable help given by Professor Bernard Benjamin, City University, and by Mr Donald N. Ross, National Heart Hospital.

Appendix I

A particular feature of the actuarial method is that the time since operation is divided into intervals of convenient length. Without loss of generality, we shall consider the case where the intervals are of length one year.

If we let x denote the number of years since operation, and if we consider the year of follow-up between x and x+1, then

let l_x be the number of patients alive at the beginning of the interval

let d_x be the number of deaths during that interval

let w_x be the number of withdrawals during that interval (i.e. number of patients lost, number of patients removed, and number of patients alive at the closing date which intervened during that interval).

Then $l_{x+1} = l_x - d_x - w_x$. And a life table may be constructed.

Let E_x be the effective number of patients exposed to the risk of dying during that interval.

Then E_x is not equivalent to l_x, since the withdrawals, w_x, who have not completed the interval of observation under consideration must not be credited with having done so. All living patients will be found surviving an incomplete interval in their latest year of follow-up except those rare cases whose anniversary of operation coincides with the closing date of the study or date of loss or removal.

In order to reach an expression for E_x we need to make some assumptions about the times of withdrawals for the w_x group. We shall assume that the withdrawn patients in the interval x to x+1 are exposed to the risk of dying on average for half that interval, so that

$$E_x = l_x - \tfrac{1}{2} w_x.$$

Then, the actuarial estimate of the probability of dying in the interval x to x+1 for a patient alive at x is q_x where

$$q_x = \frac{d_x}{E_x}$$

The estimate of the probability of surviving from x to x+1 is p_x where $p_x = 1 - q_x$ and the estimate of the (cumulative) probability of surviving from o to x is P_x where

$$P_x = p_0, p_1, p_2 \ldots p_{x-1} \text{ and } (P_0 = 1)$$

A graph of P_x plotted against x constitutes the survival curve.

A large sample approximate formula for the standard error of P_x, due to Greenwood (1926), is

$$SE\,(P_x) = P_x \sqrt{\sum_{n=0}^{x-1} \frac{d_n}{E_n(E_n - d_n)}}$$

This may be used for constructing confidence intervals for a particular P_x.

Thus, approximate 95 per cent confidence limits for P_x would be

$$P_x \pm 1{\cdot}96\ SE(P_x).$$

The difference between two independent survival curves, represented by ${}^aP_x$ and ${}^bP_x$ (for example, relating to different valves), may be tested by considering the difference between the two cumulative survival probabilities.

An approximate statistical test is to compute z and compare this with tabulated values of the standard normal distribution, where z is given by

$$z = \frac{{}^{a}P_x - {}^{b}P_x}{\sqrt{(\mathrm{SE}\,({}^{a}P_x))^2 + (\mathrm{SE}\,({}^{b}P_x))^2}}$$

Although the time intervals used hitherto have been annual, unequal intervals cause no problems and may be preferable for the early period after operation (Merrell and Shulman, 1955).

Concerning the derivation of E_x above, we have implicitly assumed that the withdrawals are subject to the same probability of dying subsequent to the last date of contact as those with complete follow-up information. This may be reasonable for those cases who are still in the study population and will be available for future study. There is little reason to believe that this group will differ from those patients who have been observed for longer periods. However, this assumption may be dangerous for the losses and removals, since failure to examine a patient for any reason may be related to the patient's health. This assumption will introduce bias into the estimates q_x if the survival experience of the withdrawals is different from those who do not withdraw.

If the withdrawals had been excluded completely from the analysis, this would have involved the more stringent assumption that their survival experience from the date of operation was similar to that for cases with complete follow-up information.

The desirability of minimising the numbers of withdrawals and hence, inter alia, reducing the possible bias of the actuarial estimates is widely recognised.

It is possible to make more sophisticated allowance for the effect of withdrawals on q_x, particularly if the points of withdrawal during an interval are known exactly. But this is unlikely to be the case in surgical applications. In addition, the actuarial approach has the merits of being simple and can be justified intuitively, if, for example, one assumes that the dates of withdrawal are evenly distributed over each interval of follow-up.

In the above derivation, we have also assumed that there is no time-related trend in the probability of dying. The various values of q_x have been obtained from patients who entered the study at different points in time. We have assumed that these probabilities remain reasonably constant over time; otherwise the qualities computed have no simple interpretation.

The survival rate derived in the previous section is not an estimate of the actual survival rate but of the net or underlying rate (according to the terminology of Grunkemeier *et al.* (1975)), that would have been obtained if withdrawals were eliminated as a cause of the patient's experience being terminated. In the terminology of actuarial mathematics, it is an independent single decrement survival rate (Benjamin and Haycocks, 1970).

INSTANTANEOUS DEATH RATE

The instantaneous death rate is called the 'force of mortality' in actuarial mathematics and it is a useful index of the intensity of risk. It provides the probability of death occurring in a very small time interval after x, given that the patient has survived to time x. We shall denote our estimate of the instantaneous probability of dying at age x by μ_x. Assuming that follow-up intervals are of width one year, the value of the force of mortality at age $x+\frac{1}{2}$ may be estimated by

$$\mu_{x+\frac{1}{2}} = \frac{2q_x}{2-q_x}$$

A large sample approximation to the standard error of μ has been derived by Gehan (1969), viz

$$\mathrm{SE}\,(\mu_{x+\frac{1}{2}}) = \frac{\mu_{x+\frac{1}{2}}}{\sqrt{E_x q_x}} \cdot \sqrt{1-\tfrac{1}{4}\mu^2_{x+\frac{1}{2}}}$$

A graph of μ_x against x shows whether the risk of death per unit time remains about the same, increases or decreases, or describes a more complex curve. It draws attention to points of time at which the risk changes in intensity by effectively focussing on the gradient of the survival curve.

For intervals of width not equal to one year, the width, h, explicitly appears in both the above formulae.

MEDIAN REMAINING LIFETIME

In nearly all papers discussing life table methods an estimate of the expectations of life or mean lifetime is derived (Irwin, 1947; Kaplan and Meier, 1958; Chiang, 1968). An ambiguity arises in the determination of this estimate if some patients are alive at the end of the study. The expectation of life (which implies an idefinitely long follow-up period) cannot be calculated unless the study period is, at least for some patients, sufficiently long to cover virtually the complete span of life. Otherwise, the mean lifetime is indeterminate and is often estimated as the mean lifetime limited to N years, where N is the maximum follow-up period possible within the study. Since this is not easily interpreted, an alternative should be found: we suggest the median remaining lifetime proposed by Gehan (1969).

Estimating the median remaining lifetime is simple, descriptive, and possible if P_x is less than 0·5 at some point x, that is the study extends to a point where the probability of survival is less than 0·5. In elementary statistical textbooks, the median is recommended for describing distributions skewed to the right, and so is a natural choice in this situation. The estimate of the median remaining lifetime is m_0 where

$$m_y = y + \frac{P_y - \frac{1}{2}}{P_y - P_y + 1}$$

and y is the number of complete years up to the point where the survival curve reaches 0·5, i.e. $P_y > \frac{1}{2} > P_{y+1}$.

A large sample approximation to the standard error of this estimate is given by

$$SE(m_0) = \frac{1}{2P_y q_y \sqrt{E_0}}$$

Similarly, the estimate of the median remaining lifetime at time x after the operation is m_x where

$$m_x = y - x + \frac{P_y - \frac{1}{2}P_x}{P_y - P_{y+1}}$$

and y is the number of complete years up to the point where the survival curves reaches $\frac{1}{2}P_x$, i.e. $P_y > \frac{1}{2}P_x > P_{y+1}$.

Similarly,

$$SE(m_x) = \frac{P_x}{2P_y q_y} \cdot \frac{1}{\sqrt{E_x}}$$

For intervals of width not equal to one year, the width, h, explicitly appears in the above formulae.

ALTERNATIVE APPROACHES TO ACTUARIAL METHOD

Kaplan and Meier (1958) give a maximum likelihood estimate of the cumulative survival probability called the product limit estimate. This estimate requires knowledge of the exact times of all decrements occurring (for example losses and removals). For large samples, the actuarial method is almost equivalent to the product limit approach.

Several ways in which the partial experience of cases withdrawing can be assigned proper interval credit have been discussed by Littell (1952), Elveback (1958), and Chiang (1968). These methods are more exact than the actuarial method but the latter is conceptually easier, simpler to operate, uses an essentially intuitive approach, and, under certain conditions, the differences may become negligible. For example, Kuzma (1967) compared the actuarial method with that due to Chiang (1968) and found that the differences were negligible for survival rates and their standard errors when the loss rates were under 40 per cent and the proportion of patients withdrawn alive was less than 30 per cent. This emphasises the need for keeping the numbers withdrawing as small as possible.

Among other statistical techniques used in survival analysis, Gehan (1965) proposed an extension of the Wilcoxon non-parametric test for comparing two sets of survival data. This approach has been used by Copeland *et al.* (1977) for comparing groups of patients having had a valve replacement. In addition, Mantel (1966) has proposed a χ^2 procedure for comparing two sets of survival data in their entirety. But neither of these methods intrinsically involves the calculation of survival probabilities nor the plotting of survival curves. Both these exercises are natural for the analysis of survival data and the presentation of results. The actuarial method automatically produces these measures in the analysis of survival data.

Appendix II

The formulae described in this paper will now be used on the information from 140 freeze dried homograft valves over a 13-year follow-up period. Table 1 is the pooled data on these valves: only four of the possible complications have been considered, and some of the valves may have experienced more than one of the complications. Table 1 has been used to construct the life tables 2, 3, 4, 5, and 6.

Table 2 is the life table for fatal valve malfunctions. D represents the deaths, L the number functioning without complication, and W includes both the valves with non-fatal complications and those lost or withdrawn during the year.

Table 1 *Pooled data on 140 freeze dried homograft aortic valves used for isolated aortic valve replacement and followed for up to 13 years*

Years	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
Valves functioning without complication	140	132	122	113	104	95	82	71	58	45	32	14	4
Valve related death	6	5	5	1	3	6	3	1	3	1	3	0	0
Non-fatal complication	1	3	4	8	4	3	8	6	5	0	0	1	0
Lost/withdrawn	1	2	0	0	2	4	0	6	5	12	15	9	4
Technical failure	4	7	3	3	0	0	0	0	0	0	0	0	0
Infection	2	2	2	1	3	2	1	3	1	0	0	0	0
Degeneration	0	1	1	5	4	4	8	5	3	1	2	1	0
Thromboembolism	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 2 *Freeze dried homograft valves. Life table for fatal valve malfunctions*

Year	*D*	*W*	*L*	*E*	*q*	*p*	*P*	*SE P*	*μ*	*SE μ*
0							1·000			
1	6	2	140	139	0·043	0·957	0·957	0·017	0·044	0·018
2	5	5	132	129·5	0·039	0·961	0·920	0·023	0·040	0·018
3	5	4	122	120	0·041	0·959	0·881	0·027	0·042	0·019
4	1	8	113	109	0·009	0·991	0·873	0·028	0·009	0·009
5	3	6	104	101	0·030	0·970	0·848	0·031	0·030	0·017
6	6	7	95	91·5	0·066	0·934	0·792	0·036	0·063	0·026
7	3	8	82	78	0·036	0·964	0·761	0·038	0·037	0·022
8	1	12	71	65	0·015	0·985	0·750	0·039	0·015	0·015
9	3	10	58	53	0·057	0·943	0·707	0·043	0·059	0·034
10	1	12	45	39	0·026	0·974	0·689	0·044	0·026	0·026
11	3	15	32	24·5	0·122	0·878	0·605	0·052	0·130	0·075
12	0	10	14	9			0·605	0·052	0·00–	
13	0	4	4	2			0·605	0·052		

D, number of deaths; W, number withdrawn because of non-fatal complications and those lost to follow-up; L, number functioning without complications; E, the derived entering numbers; q, probability of deaths for a single year; p, probability of survival for a single year; P, cumulative probability of survival; SE P, standard error of P; μ, instantaneous rate of fatal valve malfunctions; SE μ, standard error of μ. μ is calculated for the half year interval and is represented so in Table and Fig. 2.

For year one:

$$
\begin{aligned}
E_1 &= L_1 - \tfrac{1}{2}(W_1)\\
&= 140 - \tfrac{1}{2}(2)\\
&= 139\\
q_1 &= \frac{D_1}{E_1}\\
&= \frac{6}{139}\\
&= 0{\cdot}043\\
p_1 &= 1 - q_1\\
&= 1 - 0{\cdot}043\\
&= 0{\cdot}957\\
P_5 &= p_0 \times p_1 \times p_2 \times p_3 \times p_4 \times p_5\\
&= 1{\cdot}000 \times 0{\cdot}957 \times 0{\cdot}961 \times 0{\cdot}959 \times 0{\cdot}991 \times 0{\cdot}970\\
&= 0{\cdot}848
\end{aligned}
$$

The standard error of P_5 is calculated from:

$$
SE\,(P_5) = P_5 \sqrt{\sum_{0}^{4} \frac{d_n}{E_n\,(E_n - d_n)}}
$$

$$
\begin{aligned}
&= 0{\cdot}848 \cdot \sqrt{\frac{6}{139\,(139-6)} + \frac{5}{129{\cdot}5\,(129{\cdot}5-5)} \times \frac{5}{120\,(120-5)} \times \frac{1}{109\,(109-1)} \times \frac{3}{101\,(101-3)}}\\
&= 0{\cdot}848 \cdot \sqrt{\frac{6}{139{\cdot}133} + \frac{5}{129{\cdot}5{\cdot}124{\cdot}5} + \frac{5}{120{\cdot}115} + \frac{1}{109{\cdot}108} + \frac{3}{101{\cdot}98}}\\
&= 0{\cdot}848 \cdot \sqrt{0{\cdot}00032 + 0{\cdot}00031 + 0{\cdot}00036 + 0{\cdot}000085 + 0{\cdot}00030}\\
&= 0{\cdot}848 \cdot \sqrt{0{\cdot}00138}\\
&= 0{\cdot}031
\end{aligned}
$$

The instantaneous death rate, μ, is calculated from:

$$
\begin{aligned}
\mu &= \frac{2q}{2-q}\\
\mu_5 &= \frac{2 \times 0{\cdot}030}{2 - 0{\cdot}030}\\
&= \frac{0{\cdot}060}{1{\cdot}970}\\
&= 0{\cdot}030
\end{aligned}
$$

The standard error for μ_5 is calculated from:

$$
\begin{aligned}
SE\,(\mu_5) &= \frac{\mu_5}{\sqrt{E_5 \cdot q_5}} \times \sqrt{1 - \tfrac{1}{4}\,(\mu_5)^2}\\
&= \frac{0{\cdot}030}{\sqrt{101{\cdot}030}} \sqrt{1 - \tfrac{1}{4}\,(0{\cdot}030)^2}\\
&= \frac{0{\cdot}030}{\sqrt{3{\cdot}030}} \times \sqrt{1 - \frac{0{\cdot}009}{4}}
\end{aligned}
$$

$$=\frac{0{\cdot}030}{1{\cdot}741}\times\sqrt{1{-}0{\cdot}002}$$
$$=0{\cdot}017\times0{\cdot}999887$$
$$=0{\cdot}017$$

Table 3 is the life table for the multiple decrement analysis of all valve complications, both fatal and non-fatal. These complications are represented as D, and W only represents those valves lost or withdrawn.

For the first year:

$$E_1=L_1-\tfrac{1}{2}\,(W)$$
$$=140-\tfrac{1}{2}\,(1)$$
$$=139\tfrac{1}{2}$$

and $q_1=\frac{D_1}{E_1},=\frac{7}{139\frac{1}{2}}=0{\cdot}050$

and $p_1=1-q_1=1-0{\cdot}050=0{\cdot}950$

and $P_5=p_0\times p_1\times p_2\times p_3\times p_4\times p_5$
$$=1{\cdot}00\times0{\cdot}950\times0{\cdot}939\times0{\cdot}926\times0{\cdot}920\times0{\cdot}932$$
$$=0{\cdot}708$$

The standard error for P_5 for all malfunctions, the instantaneous malfunction rate μ, and its standard error are calculated as for the fatal malfunctions and all the values are presented in Table 3.

The values for P from Tables 2 and 3 have been used to construct the actuarial survival curves in Fig. 1, together with the standard errors for P_{13}. Similarly, the values for μ from Tables 2 and 3 have been used for constructing Fig. 2.

Tables 4, 5, and 6 are the life tables for three types of valve malfunction, respectively, technical error, infection, and degeneration. Each type of malfunc-

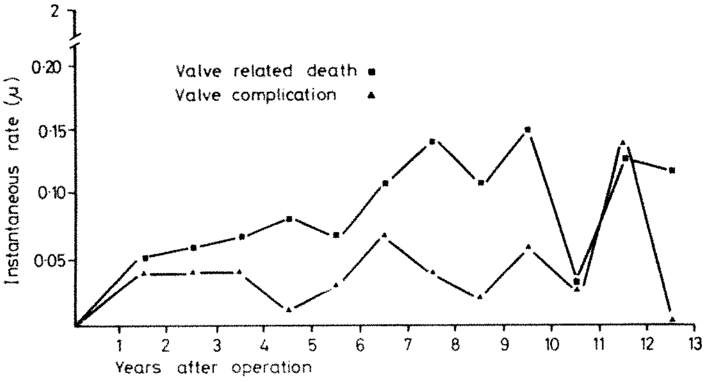

Fig. 2 *Freeze dried homograft valves. Instantaneous rate of valve related death or complication.*

Table 3 *Freeze dried homograft valves. Life table for multiple decrement analysis of all valve complications*

Year	*D*	*W*	*L*	*E*	*q*	*p*	*P*	*SE P*	*μ*	*SE μ*
0							1·000			
1	7	1	140	139·5	0·050	0·950	0·950	0·018		
2	8	2	132	131	0·061	0·939	0·892	0·026	0·051	0·019
3	9	0	122	122	0·074	0·926	0·826	0·032	0·063	0·022
4	9	0	113	113	0·080	0·920	0·760	0·036	0·077	0·026
5	7	2	104	103	0·068	0·932	0·708	0·039	0·083	0·027
6	9	4	95	93	0·097	0·903	0·640	0·041	0·070	0·026
7	11	0	82	82	0·134	0·866	0·554	0·043	0·102	0·034
8	7	6	71	68	0·103	0·897	0·497	0·043	0·144	0·043
9	8	5	58	55·5	0·144	0·856	0·425	0·043	0·109	0·041
10	1	12	45	39	0·026	0·974	0·414	0·043	0·155	·0055
11	3	15	32	24·5	0·122	0·877	0·364	0·043	0·026	0·026
12	1	9	14	9·5	0·105	0·895	0·325	0·045	0·130	0·075
13	0	4	4	2			0·325	0·045	0·111	0·111

D, all the complications; W, the valves lost to follow-up; L, the number functioning without complication; E, the derived entering number; q, the probability of any valve complication for a single year; p, the probability of freedom from any valve complication for a single year; P, the cumulative probability of freedom from any valve complication; SE P, the standard error of P; μ, the instantaneous rate of valve complication; SE μ, the standard error of μ. μ calculated to a half year interval and is represented so in Table 3 and Fig. 2.

Table 4 *Freeze dried homograft valves. Life table for valve malfunctions resulting from technical error only*

Year	*D*	*W*	*L*	*E*	*q*	*p*	*P*	*SE P*	μ	*SE* μ
0							1·000			
1	4	4	140	138	0·029	0·971	0·971	0·014		
									0·029	0·014
2	7	3	132	130·5	0·054	0·946	0·919	0·023		
									0·055	0·021
3	3	6	122	119	0·025	0·975	0·896	0·026		
									0·025	0·014
4	3	6	113	110	0·027	0·973	0·871	0·029		
									0·027	0·015
5	0									

D, the number of valves with a technical error; W, the number of valves withdrawn because of other complications or lost to follow-up; L, the number functioning without technical errors; E, the derived entering number; q, the probability of a technical error for a single year; p, the probability of freedom from a technical error for a single year; P, the cumulative probability of freedom from a technical error; SE P, the standard error of P; μ, the instantaneous rate of technical error; SE μ, the standard error of μ; μ, calculated to the half year and is represented so in Table 4 and Fig. 4.

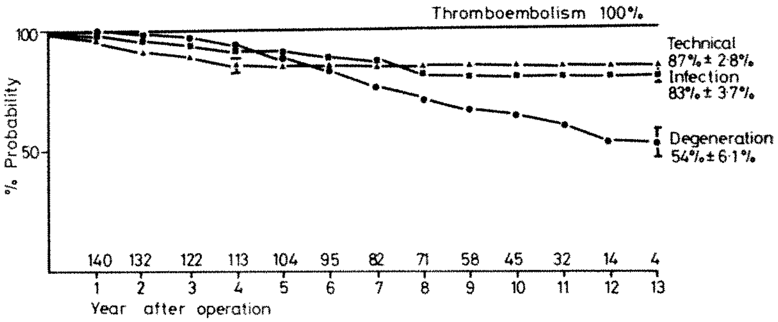

Fig. 3 *Individual complication free function curves of freeze dried homograft valves. Probabilities of freedom from thromboembolism, technical problems, infection, or degeneration.*

Table 5 *Freeze dried homograft valves. Life table for valve malfunction resulting from infection only*

Year	*D*	*W*	*L*	*E*	*q*	*p*	*P*	*SE P*	μ	*SE* μ
0							1·000			
1	2	6	140	137	0·014	0·985	0·985	0·010		
									0·014	0·010
2	2	8	132	128	0·016	0·984	0·970	0·014		
									0·016	0·011
3	2	7	122	118·5	0·017	0·983	0·954	0·018		
									0·017	0·012
4	1	8	113	109·5	0·009	0·991	0·945	0·020		
									0·009	0·009
5	3	6	104	101	0·030	0·970	0·917	0·025		
									0·030	0·017
6	2	11	95	89·5	0·022	0·978	0·896	0·028		
									0·022	0·016
7	1	10	82	77	0·013	0·987	0·885	0·029		
									0·013	0·013
8	3	10	71	66	0·045	0·954	0·844	0·035		
									0·046	0·027
9	1	12	58	52	0·019	0·981	0·828	0·037		
									0·019	0·019
10	0									
11	0									
12	0									
13	0									

D, the number of infected valves; W, the number withdrawn because of other malfunctions or lost to follow-up; L, the number of valves functioning without infection; E, the derived entering number; q, the probability of infection for a single year; p, the probability of freedom from infection; P, the cumulative probability of freedom from infection; SE P, the standard error of P; μ, the instantaneous rate of infection; SE μ, the standard error of μ; μ is calculated to the half year and is represented so in Table 5 and Fig. 4.

Table 6 *Freeze dried homograft valves. Life table for valve malfunction caused by degeneration only*

Year	*D*	*W*	*L*	*E*	*q*	*p*	*P*	*SE P*	μ	*SE* μ
0							1·000			
1	0	8	140	136	0	1·0	1·0			
									0·000	0
2	1	9	132	127·5	0·008	0·992	0·992	0·007		
									0·008	0·008
3	1	8	122	118	0·008	0·992	0·984	0·011		
									0·008	0·008
4	5	4	113	111	0·045	0·955	0·939	0·022		
									0·046	0·021
5	4	5	104	101·5	0·039	0·961	0·902	0·027		
									0·040	0·020
6	4	9	95	90·5	0·044	0·956	0·863	0·032		
									0·045	0·023
7	8	3	82	80·5	0·099	0·901	0·777	0·040		
									0·104	0·037
8	5	8	71	67	0·075	0·925	0·719	0·044		
									0·078	0·035
9	3	10	58	53	0·057	0·943	0·678	0·047		
									0·059	0·034
10	1	12	45	39	0·026	0·974	0·661	0·048		
									0·026	0 026
11	2	16	32	24	0·083	0·917	0·606	0·052		
									0·087	0·062
12	1	9	14	9·5	0·105	0·895	0·542	0·061		
									0·111	0·111
13	0	4	4	2	0	1·00	0·542	0·061		
									0·000	0

D, the number of valve malfunctions with degeneration; W, the number of valves withdrawn because of other malfunctions or lost to follow-up; L, the number of valves functioning without degeneration; E, the derived entering number; q, the probability of degeneration for a single year; p, the probability of freedom from degeneration for a single year; P, the cumulative probability of freedom from degeneration; SE P, the standard error of P; μ, the instantaneous rate of degeneration; SE μ, the standard error of μ; μ is calculated to the half year and is represented so in Table 6 and Fig. 4.

tion is entered as D, and the value for W is calculated from:

$$W_1 = L_1 - (L_2 + D_1)$$

that is for year one from Table 4

$$\begin{aligned} W_1 &= 140 - (132 + 4) \\ &= 140 - 136 \\ &= 4 \\ E_1 &= L_1 - \tfrac{1}{2}(W_1) \\ &= 140 - \tfrac{1}{2}(4) \\ &= 138 \\ q_1 &= \frac{D_1}{E_1} \\ &= \frac{4}{138} \\ &= 0{\cdot}029 \\ p_1 &= 1 - q_1 \\ &= 0{\cdot}971 \end{aligned}$$

and P and μ are calculated as before, with their respective standard errors, to give all the entries in Tables 4, 5, and 6.

The values of P from Tables 4, 5, and 6 and for thromboembolism have been used for constructing the individual event-free curves in Fig. 3 and the values of μ have been used for Fig. 4.

The median remaining lifetime can be calculated from the data in Table 2 using the formulae.

The median remaining lifetime free of complication at time 0, m_0, is calculated from:

$$m_0 = y + \frac{P_y - \frac{1}{2}}{P_y - P_{y+1}}$$

$$m_0 = 7 + \frac{0{\cdot}554 - 0{\cdot}500}{0{\cdot}554 - 0{\cdot}497}$$

$$= 7{\cdot}947 \text{ years}$$

and the standard error is calculated from

$$SE\ (m_0) = \frac{1}{2 {\cdot} P_y {\cdot} q_y} \times \frac{1}{\sqrt{E_0}}$$

$$= \frac{1}{2 \times 0{\cdot}554 \times 0{\cdot}134} \times \frac{1}{\sqrt{139{\cdot}5}}$$

$$= 6{\cdot}735 \times 0{\cdot}085$$

$$= 0{\cdot}570$$

The median remaining life time free of complication at year five, m_5, is calculated from

$$m_x = y - x + \frac{P_y - \frac{1}{2}P_x}{P_y - P_{y+1}}$$

$$m_5 = 11 - 5 + \frac{0{\cdot}364 - 0{\cdot}355}{0{\cdot}364 - 0{\cdot}325}$$

$$= 6{\cdot}231 \text{ years}$$

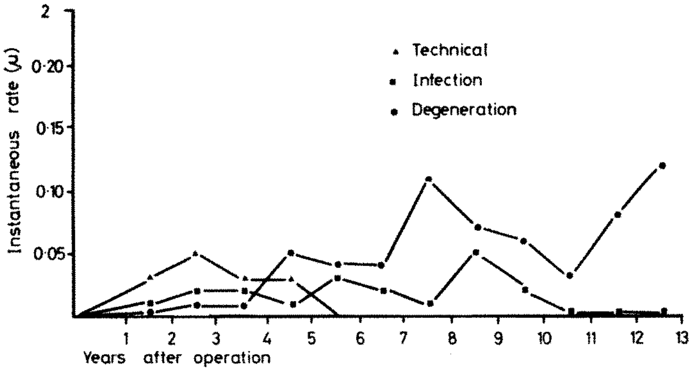

Fig. 4 *Freeze dried homograft valves. Instantaneous rate of technical problems, infection, or degeneration.*

and the standard error is calculated from:

$$\text{SE}\,(m_x) = \frac{P_x}{2 \cdot P_y \cdot q_y} \times \frac{1}{\sqrt{E_x}}$$

$$\text{SE}\,(m_5) = \frac{0 \cdot 708}{2 \times 0 \cdot 364 \times 0 \cdot 122} \times \frac{1}{\sqrt{104}}$$

$$= 7 \cdot 97 \times 0 \cdot 098$$

$$= 0 \cdot 782$$

This Appendix shows how follow-up information can be used to provide accurate data on an actuarial basis for the evaluation and comparison of different cardiac valve replacements.

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Thallium-201 imaging in assessment of aortocoronary artery bypass graft patency[1]

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SUMMARY Fifteen patients with significant coronary artery disease confirmed by cardiac catheterisation were studied before and after aortocoronary artery bypass graft surgery by rest and exercise ^{201}Tl myocardial scintigraphy in an attempt to predict graft status non-invasively. Segmental myocardial perfusion comparisons in pre- and postoperative exercise images allowed correct predictions of high ($\geq$67%) or low ($\leq$50%) graft patency rates in 10 of 15 patients, while similar comparisons in postoperative rest and exercise images yielded 13 of 15 correct predictions. Furthermore, 20 of 21 myocardial segments with increased postoperative perfusion when compared with corresponding segments in preoperative exercise studies were supplied by patent grafts. Regional graft occlusion, however, was difficult to predict. It was also difficult to predict graft status when myocardial segments were shown to have unchanged perfusion postoperatively as compared with the preoperative segmental assessment. Despite these limitations, the non-invasive technique of ^{201}Tl imaging can provide useful information regarding coronary artery bypass graft patency.

Thallium-201 has previously been shown to be a useful agent for non-invasive cardiac imaging (Bradley-Moore *et al.*, 1975; Lebowitz *et al.*, 1975). Its myocardial cell uptake depends on adequate myocardial blood flow as well as integrity of the cell membrane NA-K ATPase activity, but, nevertheless, several studies have demonstrated that ^{201}Tl distribution in the heart is proportional to local perfusion over a clinically relevant range of coronary blood flows (Strauss *et al.*, 1975; Mueller *et al.*, 1976; Strauss and Pitt, 1977; Pohost *et al.*, 1977; Weich *et al.*, 1977), suggesting a particular role for perfusion imaging in assessing patients with ischaemic heart disease. Thus, Bailey *et al.* (1977), Ritchie *et al.* (1977b), and Botvinick *et al.* (1978) have shown that comparison of rest and exercise myocardial scans with a perfusion marker such as ^{201}Tl yields useful information about both the presence and location of important occlusive lesions of the coronary arteries.

Controversy still exists about the role of aortocoronary artery bypass graft surgery in the management of ischaemic heart disease (Braunwald, 1977; Murphy *et al.*, 1977; McIntosh and Garcia, 1978). Knowledge of postoperative graft patency is necessary for evaluating the benefit of surgery in relieving cardiac pain, improving ventricular function, protecting against further myocardial infarction, and increasing longevity.

Graft patency has usually been evaluated by cardiac catheterisation, which neither lends itself to serial studies, nor is entirely free of risk. Recent studies have attempted to assess surgical results by comparing myocardial perfusion imaging using K-43 (Zaret *et al.*, 1974), Rb-81 (Lurie *et al.*, 1975), and ^{201}Tl (Ormand *et al.*, 1977; Ritchie *et al.*, 1977a; Greenberg *et al.*, 1978), with graft patency demonstrated at cardiac catheterisation.

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In this study we have investigated the potential role of ^{201}Tl imaging in the non-invasive assessment of aortocoronary bypass surgery graft patency by studying patients at rest and on exercise before and after surgery and comparing the results with pre- and postoperative coronary arteriograms and left ventriculograms.

Methods

I: PATIENTS AND PROCEDURES

Fifteen male patients, ages 42 to 64 years (mean 52), with coronary arteriograms showing greater than 75 per cent reduction in cross-sectional area in at least two coronary arteries were studied. All underwent multistage exercise treadmill testing using the Bruce procedure (Bruce *et al.*, 1973) within three months before cardiac surgery. ^{201}Tl, 2 mCi, was injected intravenously at the point of angina, $\geqslant$2 mm ST depression, maximum fatigue, or when 90 per cent of the maximum predicted heart rate was achieved. Thereafter exercise was continued for an additional 45 to 60 seconds, after which the patient was moved to an immediately adjacent room where imaging started 10 minutes after the injection, using a Searle Pho-Gamma IV scintillation camera equipped with a low-energy, high-resolution collimator and interfaced to an Ohio-Nuclear 160 data acquisition system. AP, LAO 30°, LAO 60°, and RAO 30° views were obtained in this sequence in all patients, with collection over 10 to 15 minutes of 300 000 counts per image. In 12 of the 15 patients rest images were similarly obtained, separated by at least one week from the exercise study. In the three remaining patients, four hour postexercise delayed images were taken to approximate the rest state.

Three to six months after myocardial revascularisation surgery, all patients underwent repeat cardiac catheterisation, as well as rest and exercise ^{201}Tl scans, using procedures identical to the preoperative studies (Fig. 1).

Selective coronary arteriography, biplane left ventriculography, and selective contrast injection of the grafts were performed by the Judkins technique (Judkins, 1967), and filmed in multiple projections. Arteriograms were interpreted by two experienced observers unaware of the scintigraphic data. No graft was considered occluded until attempts at both selective (in most cases utilising marker rings as guides) and non-selective (using aortograms and ventriculograms) opacification failed to show patency.

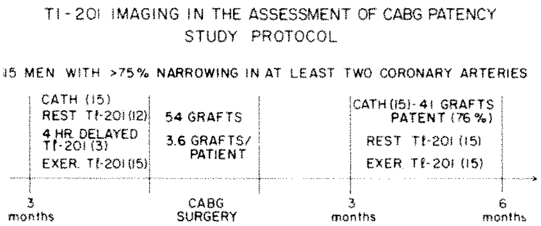

Fig. 1 *Study procedure.*

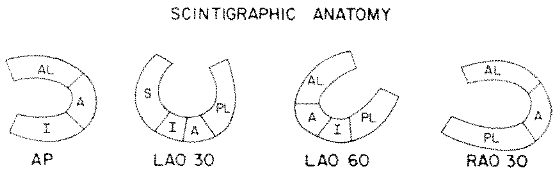

Fig. 2 *Scintigraphic anatomy in four views. A, anterior; PL, posterolateral; AL, anterolateral; S, septal; I, inferior.*

II: DATA ANALYSIS

Digital and analogue images were analysed in the unprocessed state by two experienced observers unaware of the clinical or catheterisation findings. Inter-observer disagreement was rare, and was resolved by a third experienced observer. RAO views were found to provide little diagnostic information and were, therefore, excluded from further analysis. The heart was divided into septal, inferior, apical, anterior, and posterolateral segments for scintigraphic analysis, as shown in Fig. 2. A segment was graded zero if no defect was present, 1+ if a defect occupying less than 50 per cent of that segment was present, and 2+ if the defect occupied 50 per cent or more of that segment.

New or larger postoperative exercise induced defects were identified and compared with degrees of graft patency in individual patients. Pre- and postoperative rest scans were also compared.

In addition, pre- and postoperative exercise scans, and postoperative rest and exercise scans were compared as possible predictors of the extent of postoperative myocardial revascularisation, in the following manner:

(1) Scan A was considered to show 'increased' perfusion when compared with scan B if either a net reduction in the size or the number or in both size and number of segmental perfusion defects were noted in scan A when compared with scan B.

(2) Scan A was considered to show 'decreased' perfusion when compared with scan B if either

a new increase in the size or the number or in both size and number of segmental perfusion defects were noted in scan A when compared with scan B.

(3) Scan A and scan B were felt to show 'similar' perfusion when either no change in the size or the number or in both size and number of segmental perfusion defects were noted when the two scans were compared.

Corresponding pre- and postoperative exercise scintigraphic segments were compared as possible predictors of regional graft patency. For these analyses, the blood supply of the septal segment was assumed to be from left anterior descending grafts, and apical and anterior blood supply from left anterior descending or diagonal or from both grafts. Inferior segments were felt to be supplied by right coronary artery or dominant left circumflex grafts, and posterolateral segments from left circumflex or dominant right coronary artery grafts or from both.

Perioperative myocardial infarction was diagnosed from an analysis of serial electrocardiograms and cardiac enzymes (CK) and isoenzymes (CK MB) as well as from results of pre- and postoperative technetium-99m pyrophosphate scans (Walsh *et al.*, 1977).

Table *Summary of patient data*

Case no.	*Age (y)*	*Percentage graft patency*	*Multiple-stage exercise testing (MSET)*	*Maximum$^{\circ}$ pressure—rate product*	*Graft patency rate predicted by MSET*	*New or larger perfusion defects (PD) with exercise*	*New or larger postop rest PD*	*Absent or smaller postop rest PD*	*Periop MI*
1*	54	100 (3/3)							
Preop			I	18 200		Yes			
Postop			+	26 720		No	Yes		
2	42	75 (3/4)							
Preop			+	17 040		Yes			
Postop			+	26 720		No	Yes	Yes (2)	
3	58	100 (3/3)							Inferior
Preop			I	21 000		No			
Postop			–	28 525		Yes	Yes	Yes (2)	
4	54	75 (3/4)							
Preop			+	23 200		Yes			
Postop			I	26 600		No	Yes		
5	64	33 (1/3)			Yes				
Preop			+	12 000		Yes			
Postop			+	25 575		No	Yes		
6	49	100 (5/5)			Yes				
Preop			+	22 080		Yes			
Postop			–	30 060		No			
7	62	100 (3/3)							
Preop			+	9 900		Yes			
Postop			+	19 500		Yes	Yes	Yes	
8	52	50 (2/4)							
Preop			+	21 000		Yes			
Postop			I	21 000		Yes			
9	56	100 (3/3)							
Preop			+	18 850		Yes			
Postop			I	23 200		Yes	Yes (2)	Yes	
10	54	100 (4/4)							
(P) Preop			+	21 000		Yes			
Postop			+	30 060		Yes			
11†	44	33 (1/3)							
Preop			+	20 480		Yes			
Postop			+	22 545		Yes			
12	49	75 (3/4)			Yes				
Preop			+	21 710		Yes			
Postop			–	30 060		No			
13	47	67 (2/3)			Yes				
Preop			+	20 300		Yes			
Postop			–	28 390		No	Yes		
14	53	33 (1/3)							
(P) Preop			I	10 500		Yes			Inferior
(P) Postop			I	15 000		Yes			
15	46	80 (4/5)							Anteroseptal
Preop			+	8 500		Yes			
Postop			+	23 200		No	Yes (2)	Yes	

*, Patent right coronary graft to posterior descending with 95 per cent occlusion; †, unbypassed critical LAD lesion; (P), taking propranolol; +, positive; –, negative; I, inconclusive; $^{\circ}$, mean of peak blood pressure in mmHg × maximum achieved heart rate/min.

Results

(A) SURGICAL RESULTS

Fifty-four grafts were placed at surgery in the 15 patients (average = 3·6 grafts/patient), of whom eight had three, five had four, and two had five grafts positioned. Fifty-two were saphenous vein, and two internal mammary bypass grafts. At repeat catheterisation three to six months after operation 41, or 76 per cent were patent. All patients had at least one, and 12 of the 15 had two or more grafts patent at the time of restudy. Angina was much improved or absent in 14 of the 15 patients after operation.

(B) MULTIPLE-STAGE EXERCISE TESTING

Using ≥1·0 mm of horizontal or downsloping ST segment depression measured 80 ms after the J point of the electrocardiogram as the criterion for a positive response, reversion of a preoperative positive to a postoperative negative multistage exercise test predicted graft patency rates of ≥67 per cent in three patients, while a newly positive postoperative multiple stage exercise testing indicated ≤50 per cent graft patency in one patient. In the remaining 11 patients, however, exercise testing failed to provide any clear indication of graft status (Table).

The level of exercise performed, as shown by pressure-rate products (peak systolic blood pressure in mmHg × maximum achieved heart rate/minute), increased significantly in 14 of the 15 patients in postoperative tests. Preoperatively, pressure-rate products ranged from 8500 to 23 200, with a mean of 17 717, rising postoperatively to a range of 15 000 to 30 060, and a mean of 25 143.

Two patients were exercised while taking propranolol before surgery, and one of these remained on this drug at the time of postoperative exercise testing; no patient was exercised while on digoxin (Table).

(C) NEW OR LARGER EXERCISE-INDUCED ^{201}TL PERFUSION DEFECTS

New or larger perfusion defects were noted in 14 of 15 patients in preoperative exercise and 7 of 15 patients in postoperative exercise ^{201}Tl scans when compared with corresponding images in the rest state. Three of these seven patients who developed such defects with exercise postoperatively had ≤50 per cent graft patency, compared with one patient with ≤50 per cent graft patency among those eight patients without new or larger exercise-induced postoperative perfusion defects.

(D) COMPARISON OF PRE- AND POSTOPERATIVE ^{201}TL REST SCANS

Analysis of the postoperative rest ^{201}Tl scans revealed 11 segments in nine patients with new or larger perfusion defects when compared with corresponding segments in the preoperative rest scans. Perioperative myocardial infarction in the distribution of these particular segments was documented in two of these nine patients (Table); 10 of 11 segments were supplied by patent grafts.

In contrast, seven segments in five patients showed smaller or absent postoperative rest ^{201}Tl defects when compared with preoperative studies. None of these patients developed perioperative myocardial infarctions nor were graft occlusions in the distribution of these segments shown in any (Table).

Fifty-seven segments were unchanged in postoperative rest scans when compared with corresponding preoperative rest studies.

(E) COMPARISON OF PRE- AND POSTOPERATIVE EXERCISE ^{201}TL AS PREDICTOR OF EXTENT OF MYOCARDIAL REVASCULARISATION

Fig. 3 depicts the relation between a comparison of pre- and postoperative exercise scans and percentage graft patency. All eight patients in whom postoperative exercise scans showed 'increased' perfusion when compared with the preoperative exercise study had high graft patency rates (≥67%). Five patients with 'similar' perfusion in pre- and postoperative exercise scans had graft patency rates ranging from 33 to 100 per cent, whereas both patients with 'decreased' perfusion postoperatively had low graft patency rates (≤50%).

Fig. 4 shows pre- and postoperative exercise ^{201}Tl scans from a patient with 75 per cent graft patency. Postoperative perfusion was judged to be 'improved', since a large inferior defect noted preoperatively is now smaller, and large apical and posterolateral defects are no longer present in the postoperative exercise scan as compared with the preoperative study.

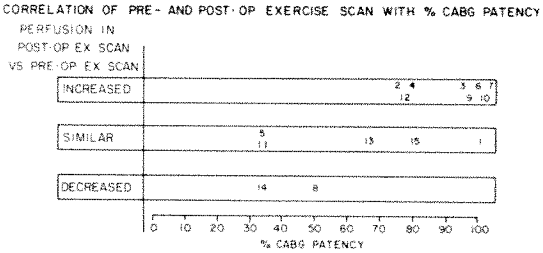

Fig. 3 *Correlation of pre- and postoperative exercise scans with percentage graft patency.*

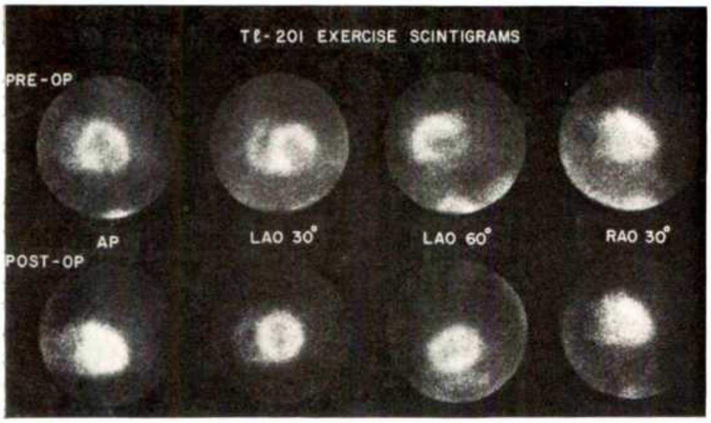

Fig. 4 ^{201}*Tl pre- and postoperative exercise myocardial scintigrams from a patient in whom three of four grafts were patent showing improved uptake in the inferior, apical, and posterolateral regions.*

(F) COMPARISON OF POSTOPERATIVE REST AND EXERCISE ^{201}TL AS PREDICTOR OF EXTENT OF MYOCARDIAL REVASCULARISATION

Fig. 5 depicts the relation between a comparison of postoperative rest and exercise scans and percentage graft patency. In 11 patients with 'increased' or 'similar' perfusion in postoperative exercise scans when compared with postoperative rest studies, 10 had two-thirds or more of their grafts patent (1 to 67%, 3 to 75%, 1 to 80%, 5 to 100%); in four patients with 'decreased' postoperative exercise perfusion when compared with the resting state, three had one-half or less of their grafts patent (2 to 33%, 1 to 50%).

Fig. 6 shows identical postoperative rest and exercise scans and, therefore, 'similar' perfusion in a patient with 100 per cent graft patency. An apical defect present at rest is unchanged after exercise; no new exercise-induced defects are noted.

Since each patient is designated by the same number in all Figures and in the Table, it should be noted that the degree of graft patency, which could not be judged by pre- and postoperative exercise scan comparison in five patients (cases 1, 5, 11, 13, 15), was correctly predicted in four of this group (cases 1, 11, 13, 15) by comparing the postoperative exercise scan with the postoperative rest study. One patient (case 10) had graft patency correctly pre-

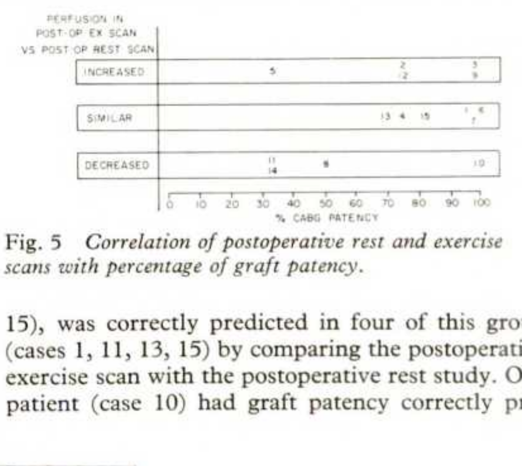

Fig. 5 *Correlation of postoperative rest and exercise scans with percentage of graft patency.*

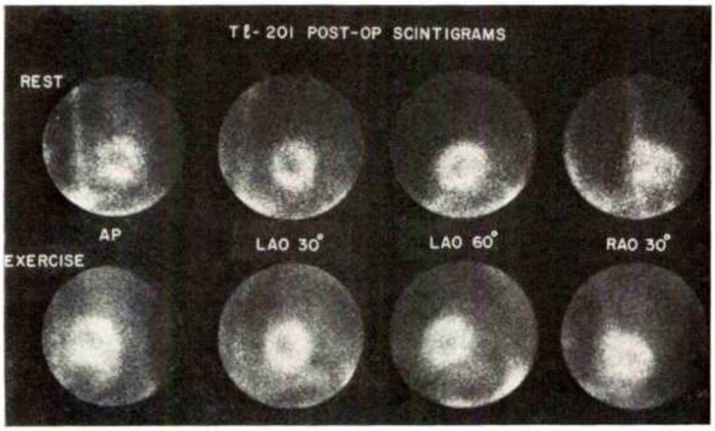

Fig. 6 ^{201}*Tl postoperative rest and exercise myocardial scintigrams—all grafts patent.* Note—*the apical defect present at rest remains unchanged on exercise.*

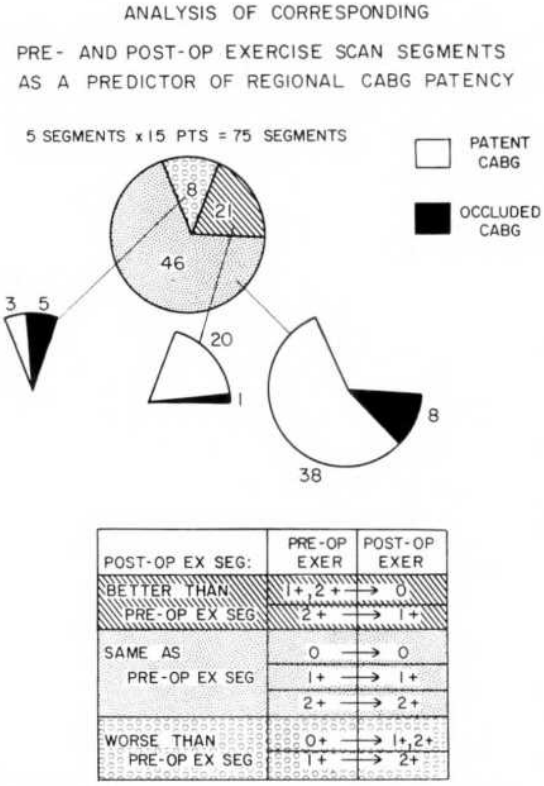

Fig. 7 *Value of corresponding pre- and postoperative myocardial scintigraphic segments as predictors of graft patency.*

dicted by pre- and postoperative exercise scan comparison and not by postoperative rest-exercise analysis. In nine patients (cases 2, 3, 4, 6, 7, 8, 9, 12, 14), graft patency was correctly predicted by both methods.

(G) COMPARISON OF PRE- AND POSTOPERATIVE EXERCISE SEGMENTS AND REGIONAL GRAFT PATENCY

Fig. 7 shows the relation between a comparison of corresponding pre- and postoperative exercise segments and patency in grafts defined as supplying those specific segments (see Methods). Of 21 postoperative segments having a grading better than the corresponding preoperative exercise segment, 20 were supplied by patent grafts. Of eight postoperative segments having a worse grading than the corresponding preoperative exercise segment, five were supplied by occluded grafts; 38 of 46 segments unchanged postoperatively were supplied by patent grafts.

In Fig. 8 large apical and inferior preoperative exercise-induced defects, respectively, are smaller and absent in the postoperative exercise scan. Both segments were supplied by patent grafts.

Discussion

This study confirms the useful role of myocardial perfusion imaging in the non-invasive assessment of coronary artery bypass graft patency. High ($\geq 67\%$) or low ($\leq 50\%$) graft patency rates were correctly predicted in 13 of 15 patients (87%) from postoperative rest-exercise scan analysis. This compared with only four of 15 (27%) correct predictions using pre- and postoperative multistage exercise electrocardiographic data.

Initially, we had expected that new or larger postoperative exercise-induced defects would closely correlate with significant graft occlusion, as has been shown by other investigators (Ritchie *et al.*, 1977a; Greenberg *et al.*, 1978). However, we found only a weak association (3/7 with significant graft occlusion if such defects were present *vs.* 1/8 if they were not) between these variables. Occlusive lesions

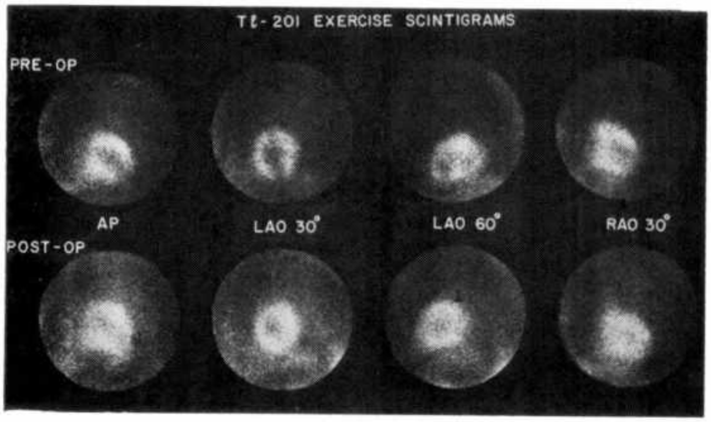

Fig. 8 *^{201}Tl pre- and postoperative exercise myocardial scintigrams. Apical and inferior uptake defects before operation are respectively smaller or absent after surgery. Both segments were supplied by patent grafts.*

in coronary arteries which were not bypassed or patent grafts to coronary arteries with significant occlusions distal to the sites of anastomoses, both uncommon in our study (Table), have been suggested as possible explanations for new postoperative exercise-induced defects in patients with patent grafts (Ritchie *et al.*, 1977a). Four of seven patients with such defects did not have significant graft occlusion; in fact, we were surprised to note that in all four patency of all the grafts positioned was found at the postoperative catheterisation studies. This suggests that despite patent grafts, certain patients may still develop new or larger perfusion defects on exercise possibly as a result of regional maldistribution of blood flow at high myocardial work loads. As already noted, 14 of 15 patients were able to perform greater amounts of exercise in the postoperative as compared with preoperative multistage exercise treadmill testing studies.

A further unexpected finding was 11 new or larger segmental postoperative rest defects in nine patients. Only two of these developed perioperative myocardial infarction in the distribution of the segment in question, and 10 of 11 of these segments were supplied by patent grafts. One explanation for this phenomenon is that the increased ^{201}Tl uptake in the adjacent myocardium as a result of enhanced blood flow via patent grafts may have caused small or difficult to recognise preoperative resting defects easier to recognise postoperatively because of the greater relative difference in counts between the two areas which followed aortocoronary artery bypass graft surgery. On the other hand, Bulkley and Hutchins (1977), who studied the hearts of patients dying soon after surgery, noted areas of myocardial damage in the distribution of patent grafts suggesting the possibility of reperfusion necrosis occurring in segments of the myocardium subjected to a sudden new blood flow through the graft at the end of cardiopulmonary bypass. It is possible, therefore, that intraoperative myocardial injury, not recognisable by infarct detection techniques currently in use, may be responsible for some of these new or larger postoperative rest defects; cardiac imaging, therefore, may have an important additional role in assessing techniques for the preservation of myocardial integrity during surgery.

In contrast, we presume that the seven segments in the five patients with smaller or absent postoperative rest defects when compared with preoperative rest studies represent regions of the myocardium with improved postperative resting flow. No perioperative myocardial infarction occurred in these patients, and all the segments were supplied by patent grafts.

Eight patients had 'increased' perfusion in the postoperative exercise scans. All had high graft patency rates, and all were able to achieve a higher exercise load postoperatively. In contrast, the two patients with 'decreased' perfusion had low graft patency rates. No clear pattern of graft patency emerged in the five patients with 'similar' perfusion in pre- and postoperative exercise scans (Fig. 3).

When postoperative rest and exercise scans were compared, 10 of 11 patients with 'similar' (six patients) or 'increased' (five patients) perfusion had high graft patency rates (1 to 67%, 3 to 75%, 1 to 80%, 5 to 100%); three of four with 'decreased' perfusion had a low patency rate (2 to 33%, 1 to 50%) (Fig. 5). The phenomenon of smaller or absent perfusion defects with exercise, which may be secondary to increased postoperative perfusion through patent grafts or via collaterals, has been noted previously (Strauss and Pitt, 1977). Whatever the mechanism, our results support the assumption that patients showing this phenomenon, as well as those who have no decrease in perfusion in postoperative rest and exercise scan comparisons, probably have patent grafts. Those whose postoperative studies show diminished perfusion with exercise are likely to have occluded or poorly functioning grafts.

Recognising that our assigning blood flow from specific coronary bypass grafts to scintigraphic segments is arbitrary, nevertheless, no fewer than 20 of 21 segments with smaller or absent perfusion defects in postoperative exercise segments were actually supplied by patent grafts. Prediction of occluded grafts was, however, unreliable, being present in five of eight segments with larger postoperative exercise defects when compared with preoperative exercise studies. No predictions could be made regarding graft patency in the 46 segments demonstrating no change in perfusion in pre- and postoperative exercise scans (Fig. 7).

Several limitations of our approach to the noninvasive predictions of graft patency should be recognised. First the selection of $\geqslant$67 per cent as high and $\leqslant$50 per cent as low graft patency is clearly arbitrary, and may have little clinical meaning for the individual patient with postoperative chest pain. As can be seen from Fig. 3 and 5, however, these criteria do represent a natural division in our data, and may be useful for group analysis. In addition, though the results of this study are in general agreement with previously published reports (Ormand *et al.*, 1977; Ritchie *et al.*, 1977a; Greenberg *et al.*, 1978), the number of patients in all of these studies, including our own, is small, indicating the need for further comparative studies. The cost of ^{201}Tl myocardial scintigraphy is not trivial, and a high degree of sensitivity and specificity will have to be shown before this or similar isotopic imaging techniques can be accepted as a standard diagnostic procedure. Finally, the ability of imaging to predict regional graft patency was limited to 21 of 75 segments and the technique failed to predict graft occlusion reliably. In 46 of 75 segments imaging could not indicate graft status.

Despite these problems we were able in this study to predict high and low degrees of graft patency in 10 of 15 patients by comparing pre- and postoperative exercise ^{201}Tl scans, and in 13 of 15 patients by postoperative rest and exercise scan comparisons. As noted above, while regional graft patency could be assessed by the finding of a smaller or absent segmental postoperative exercise defect compared with the corresponding preoperative exercise segment, regional graft occlusion could not be reliably predicted. New or larger perfusion defects occurring in postoperative exercise scans were not by themselves sufficient to predict graft status.

Thus at present it appears that high rates of graft patency can now be separated from low patency rates by ^{201}Tl imaging. The development of further refinements in imaging techniques should permit this type of investigation to provide the clinician with a reliable method of evaluating the results of aortocoronary bypass graft surgery in a non-invasive fashion.

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Thallium-201 myocardial imaging in evaluation of asymptomatic individuals with ischaemic ST segment depression on exercise electrocardiogram[1]

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SUMMARY Asymptomatic adults with normal physical examination, normal resting electrocardiogram, and normal routine laboratory evaluation who have a positive exercise electrocardiogram and abnormal exercise thallium-201 myocardial image have a very high probability of angiographically significant coronary artery disease. If, on the other hand, the exercise electrocardiogram is positive for 'ischaemic' ST segment changes, but the exercise thallium image is normal, the probability for coronary disease is low. The exercise electrocardiogram combined with thallium-201 myocardial image are safe non-invasive methods which can be performed on an out-patient basis.

The ST segment response on the exercise electrocardiogram has been increasingly used as a method to detect individuals with ischaemic heart disease. Its popularity is based on epidemiological studies (Bruce and McDonough, 1969; Doyle and Kinch, 1970; Froelicher *et al.*, 1974; Aronow and Cassidy, 1975) of asymptomatic subjects with positive ST segment response to exercise, predicting a higher risk of developing myocardial ischaemic events over the next several years. However, the predictive accuracy of a positive exercise electrocardiogram in asymptomatic individuals who agreed to have coronary arteriographic studies performed is less than 53 per cent (Froelicher *et al.*, 1973; Borer *et al.*, 1975).

Thallium-201 myocardial imaging has recently been shown to be a sensitive method to detect transient myocardial ischaemia (Bailey *et al.*, 1977). Thallium-201 has biological properties similar to potassium-43 (Zaret *et al.*, 1973) and is taken up by viable myocardial cells with an intact sodium-potassium ATPase system in proportion to myocardial blood flow in accordance with the Sapirstein principle (Sapirstein, 1956). Areas of myocardial ischaemia can be detected by a relative decrease in regional tracer uptake (Strauss *et al.*, 1973). The present study was undertaken in an effort to determine whether thallium-201 (^{201}Tl) myocardial imaging at rest and during maximal exercise is useful in the evaluation of asymptomatic patients with a positive exercise electrocardiogram.

Patients and methods

Out of 3496 consecutive treadmill exercise tests performed primarily on asymptomatic patients, 22 asymptomatic individuals with normal physical examination developed 2 mm or more horizontal ST segment depression on the electrocardiogram during maximal exercise. These individuals had routine laboratory studies, chest *x*-ray films, resting electrocardiogram both in the supine and standing position and after hyperventilation all of which were normal. The ST depression during exercise testing was not associated with chest pain or any other angina-like symptoms. Fifteen of these 22 patients agreed to be evaluated further. There were 14 men and one woman with a mean age of 53 years (range 27 to 62 years). The female patient had a history of episodic ventricular tachycardia.

MYOCARDIAL IMAGING

Thallium-201[2] was administered intravenously in a dose of 1·5–2 mCi for both the rest and exercise myocardial studies with the patient fasting and upright to minimise hepatic and gastric concentration.

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[2] Thallium-201 (thallous chloride) was supplied as a sterile pyrogen-free radiopharmaceutical in 0·9 per cent saline at *p*H 5–6 in a specific activity of 1 mCi/ml (Philips-Duphar or New England Nuclear). The half life of the isotope is 72 hours. The radiation burdens are: 0·7 rads/mCi whole body, and to the target organs, kidney, and gonads 0·5 rads/mCi (Cook *et al.*, 1976).

Myocardial imaging began 10 minutes after the tracer administration. Images were recorded with the patient supine in the anterior view, 40 and 60 degree left anterior oblique views (obtained by rotating the detector). This procedure (Bailey *et al.*, 1977) facilitated comparison of each rest view with each view obtained after exercise. A 37 photomultiplier tube Anger type scintillation camera (Ohio Nuclear Series 100) equipped with high resolution parallel hole collimator was used. Images were recorded with a 20 per cent window centred on the mercury *x*-ray peaks (69–80 keV). A total of 50 000 counts was recorded in the region of the myocardium (approximately 200–300 000 counts/image) to minimise the statistical fluctuations in the thallium image. This resulted in a count density of at least 1000 counts/cm^2 over the region of the left ventricular myocardium. Images were recorded into an Ohio Nuclear Series 150 data system after uniform field correction and stored on magnetic tape. Imaging in each of the views required 8 to 12 minutes. The rest and exercise studies were performed one week apart. The patients were familiarised with the exercise procedure during a previous visit. An indwelling Teflon cannula was inserted percutaneously into a forearm vein and kept patent with a slow infusion of saline to facilitate injection of tracer during exercise. Exercise was carried out in the imaging laboratory using an electrically braked Godart bicycle ergometer according to the following procedure. After an initial warm-up period of cycling without workload, the load was set at 50 watts and then increased by 25 watt increments every three minutes until further exercise was limited by breathlessness, fatigue, or the occurrence of an arrhythmia. ^{201}Tl was injected at peak exercise and patients were encouraged to maintain a constant level of exercise for an additional one minute. Continuing exercise after tracer injection was important in order to achieve the state during which the majority of the tracer is cleared from the blood. The electrocardiogram and systemic pressure were monitored throughout the exercise and the recovery periods. The subjects remained seated on the bicycle while the post-exercise electrocardiograms were recorded. When electrocardiograms were completed, the patient was placed supine beneath the scintillation camera and imaging was started. The time interval between thallium-201 myocardial imaging and coronary arteriography was less than six weeks in all patients. No clinical coronary event occurred between any of the studies. The electrocardiogram was recorded in the same fashion as described earlier.

The myocardial images were interpreted by two observers before coronary arteriography was carried out. Images from the study patients and known normal subjects were randomly mixed. All the resting images were normal, showing a homogeneous tracer distribution in the region of the left ventricular myocardium. A normal variant pattern includes somewhat decreased uptake of radionuclide in the apical region, probably resulting from the geometry of the left ventricle. This variant pattern has been seen in about 20 per cent of normal individuals (Zaret, 1977). To determine the percentage of the left ventricle that was involved by a tracer defect, the outline of the left ventricle in each projection was traced. The area of decreased tracer uptake was then superimposed on the left ventricular outline and expressed as a percentage of the left ventricular circumference, excluding the region of the aortic valve plane in the anterior projection, and the aortic and mitral valve planes in the left anterior oblique projection. A previous investigation (Cook *et al.*, 1976) has disclosed that normal individuals may have small regions of decreased tracer concentration at the apex, as mentioned above, or at the region of insertion of the mitral valve on the high posterolateral wall of the left ventricle. The exercise myocardial ^{201}Tl image was evaluated in a similar fashion. The pair of rest and exercise studies was examined together and considered positive for ischaemia only if a new perfusion defect involving more than 15 per cent of left ventricular circumference appeared during exercise and had not been present at rest.

CARDIAC CATHETERISATION AND CORONARY ARTERIOGRAPHY

Cardiac catheterisation, left ventriculography, and selective coronary arteriography were performed in multiple projections using the modified Judkins technique (1967). Each study was reviewed by an independent observer with no knowledge of the myocardial scan. A patient was considered to have one, two, or three vessel disease depending on whether one, two, or all three major arteries of their branches contained narrowings of 70 per cent or more of the respective luminal area. A narrowing of greater than 70 per cent in the main left coronary artery was considered as a significant narrowing of both the anterior descending and circumflex coronary arteries.

All electrocardiograms, and ^{201}Tl myocardial images and angiograms were technically adequate for evaluation. Informed consent was obtained from all volunteers and there were no complications resulting from any of these procedures.

Results

All exercise electrocardiograms both during tread-

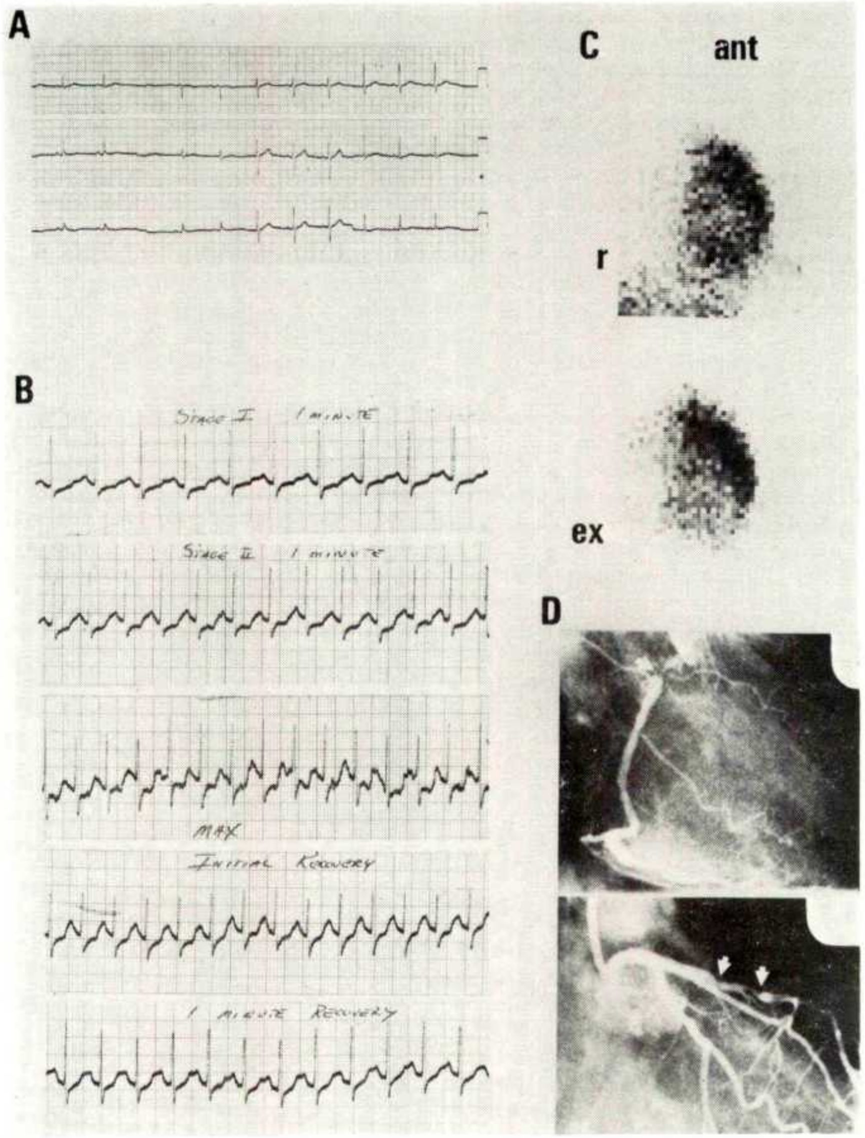

Fig. 1 *Findings in a 61-year-old asymptomatic man. (A) Normal electrocardiogram at rest. (B) Abnormal exercise electrocardiogram showing 3 mm horizontal ST depression, rate 165/min, lead V5. (C) Thallium-201 myocardial scan at rest (r) and exercise (ex) in the anterior (ant) and 60° left anterior oblique projections. The rest study shows a relatively uniform pattern of tracer uptake in the left ventricular myocardium. The exercise study shows a perfusion defect involving the inferior wall. (D) Selective coronary arteriography from the same patient. The right coronary artery (top) is totally occluded, proximally, and the left anterior descending artery has high grade occlusive lesions proximally (arrows) in this asymptomatic man with a 'dominant right coronary circulation'.*

mill testing and on the bicycle ergometer, done at different times, exhibited 2 mm or more horizontal ST depression in lead V5. All patients had a normal homogeneous pattern of ^{201}Tl uptake at rest.

Of the 15 asymptomatic individuals with horizontal ST depression on exercise testing, five had

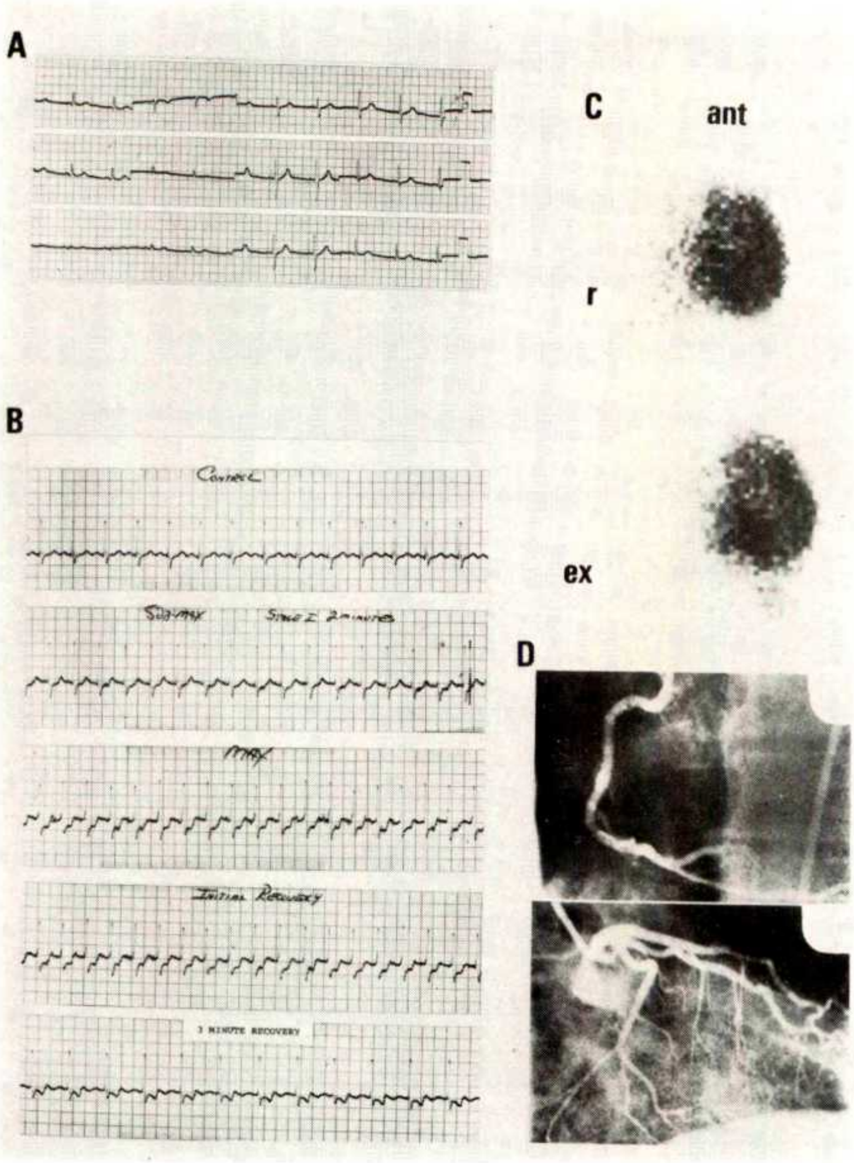

Fig. 2 *Findings in a 65-year-old asymptomatic man. (A) Normal electrocardiogram at rest. (B) Abnormal exercise electrocardiogram showing 3·5 mm horizontal ST depression, rate 152/min, lead V5. (C) Thallium-201 myocardial scan at rest (r) and exercise (ex) in the anterior (ant) and 60° left anterior oblique projections. The rest study shows a relatively uniform pattern of tracer uptake in the left ventricular myocardium. The exercise study showed no radiopenic areas in any projection. (D) Selective coronary arteriography from the same patient. The right coronary artery (top) is normal. The left coronary arterial system (bottom) is free of any occlusive lesions.*

normal ^{201}Tl myocardial image after exercise while 10 individuals developed new defects in tracer uptake. Four of the five individuals with a normal exercise thallium-201 image had normal coronary arteriograms and only one had an abnormal coronary arteriogram. This patient had a high grade occlusive lesion of the main left coronary artery and near total occlusion of the proximal right coronary artery. Of the 15 study patients, 10 had abnormal ^{201}Tl images after exercise as judged by the appearance of new defects in tracer uptake; nine of these had significant coronary narrowing of two or more major coronary vessels at angiography while one patient with an abnormal exercise ^{201}Tl myocardial image had minimal irregularities of the left anterior descending artery.

Discussion

The identification of patients with asymptomatic coronary artery disease is important.

It had been hoped that in asymptomatic persons with a normal electrocardiogram at rest, a compromised coronary circulation may be detected by an exercise test. Unfortunately, less than 50 per cent of 'positive' exercise electrocardiograms in asymptomatic subjects accurately reflect significant coronary disease by arteriography (Borer *et al.*, 1975).

The results of the present study suggest that exercise ^{201}Tl myocardial image has a higher predictive value than ST segment depression alone on the exercise electrocardiogram in detecting myocardial ischaemia in asymptomatic individuals with coronary artery disease.

Of the 15 patients who were positive for ischaemic ST changes on exercise electrocardiogram, five had normal exercise ^{201}Tl myocardial image and 10 had abnormal ^{201}Tl myocardial image. Four of the five individuals with normal myocardial image at peak exercise also had normal coronary arteries by angiography. However, one patient with a normal ^{201}Tl myocardial image had high grade occlusive lesions of the main left coronary artery and the proximal right coronary artery. This was a false negative myocardial image. The diagnostic criterion for a positive myocardial image is based on the appearance of new myocardial defects in tracer uptake after exercise. Tracer uptake was probably uniformly reduced in this patient. This homogeneity of myocardial perfusion in some patients with triple vessel coronary disease has been noted before for both ^{201}Tl (Bailey *et al.*, 1977) and other cationic tracers (Hall *et al.*, 1975). Ten patients had an abnormal exercise ^{201}Tl myocardial image. Nine out of 10 had significant coronary disease by angiography and one had minimal and insignificant lesions in the anterior descending system. The finding of a positive exercise myocardial image in an asymptomatic patient with a positive exercise electrocardiogram makes the probability of obstructive coronary disease extremely likely.

In such an asymptomatic patient with both a positive exercise electrocardiogram and thallium-201 myocardial image we advise risk factor reduction and further follow-up. Coronary arteriography should be reserved until the patient becomes symptomatic and is considered a candidate for coronary artery bypass graft surgery. The role of coronary arteriography in the situation in which the exercise electrocardiogram is positive and the exercise myocardial thallium-201 image negative is more difficult to determine. As pointed out above, this combination reduces but does not eliminate the possibility of significant coronary artery disease. In an individual with a high risk occupation such as a pilot in whom uncertainty as to diagnosis cannot be tolerated, arteriography may be indicated. In other individuals, however, we would determine the need for arteriography depending upon individual circumstances. The addition of exercise, blood pool imaging to detect myocardial ischaemia (Borer *et al.*, 1977) in such a situation may further increase the certainty of the presence or absence of significant coronary artery disease and the need for coronary arteriography.

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Whole body potassium and total exchangeable potassium in elderly patients with cardiac failure

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SUMMARY Body potassium status of patients with cardiac failure may be estimated by a number o methods, but increasing reliance is being placed upon radioisotope dilution with ^{42}K which measures the total exchangeable potassium. Total exchangeable potassium comprises between 86 per cent and 97 per cent of whole body potassium in healthy subjects. We have measured total exchangeable potassium in 22 oedema-free elderly patients with stable cardiac failure and compared the results with simultaneously determined measurements of whole body potassium obtained by whole body counting. The mean whole body potassium was 2360±640 mmol. The mean value of total exchangeable potassium measured at 24 hours was 1820±610 mmol (77% of whole body potassium) and increased further to 2000±600 mmol (84%) when measured after 48 hours. In patients with cardiac failure and, perhaps, also other patients with a history of fluid retention, the mixing of a tracer dose may be significantly delayed, which if not appreciated may lead to an overestimate of potassium depletion.

A number of studies (White *et al.*, 1969; Davidson and Gillebrand, 1973; Nicholls *et al.*, 1976) reported in the past decade have suggested that potassium depletion is common in patients with cardiac failure. A recent review (*British Medical Journal*, 1977) emphasised that elderly patients should be considered to be especially at risk because of poor dietary intake of potassium, and concluded that potassium supplementation is mandatory for elderly patients in heart failure, particularly those taking long-term diuretics. In all these studies body potassium status has been estimated from measurements of the total exchangeable potassium obtained by radioisotope dilution using ^{42}K or ^{43}K. These studies have suggested an average deficit of potassium content in cardiac failure of approximately 30 per cent. The reference values (especially pre-morbid, predicted, or actual body weights) used in these studies have not been uniform and it may well be that differences in estimated depletion are related to these factors. In general, the measurements are based on spot urine samples taken at hourly intervals from 24 hours after administration of the isotope. In only one case (Novak and Harrison, 1973) were samples taken as late as 36 hours. The radioisotope dilution method requires that equilibration should have occurred between the body otassium and the tracer; in healthy subjects this occurs in 24 hours (Corsa *et al.*, 1950). However, since 1957 there have been a number of papers suggesting that in certain clinical conditions equilibration may be significantly delayed. O'Meara *et al.* (1957) suggested that this occurred in patients with fluid retention. Boddy *et al.* (1972b) investigated patients with chronic renal failure. By using the longer half-life isotope ^{43}K and taking samples up to 64 hours after giving the tracer, they found that equilibration was significantly delayed. The same group of workers (Boddy *et al.*, 1978) also found delayed equilibration in patients with chronic bronchitis. Therefore, the effect of basing an estimate of exchangeable potassium on samples taken at around 24 hours may well underestimate the true value of body potassium. Only three studies have so far been reported in which the total body potassium of patients in cardiac failure has been measured by counting ^{40}K in a whole body counter. The deficits of body potassium content were reported as being 10 per cent by Delwaide and Rorive (1973); 5 per cent by Davidson *et al.* (1976); and Lawson *et al.* (1976) found no significant deficit.

The discrepancy in the findings using the two methods may in part be accounted for by the problem of delayed equilibration in the measurement of exchangeable potassium. To investigate this hypothesis we have measured both the whole body potassium and the exchangeable potassium in

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elderly patients with controlled cardiac failure. From the two measures of body potassium we also obtained the value of exchangeable potassium as a proportion of whole body potassium. This ratio in healthy volunteers measured at 24 hours has been reported to have an average value of 93 per cent with a range of 86 to 97 per cent (Rundo and Sagild, 1955; Talso *et al.,* 1960; Surveyor and Hughes, 1968). Only one study has investigated this ratio in healthy elderly subjects where it was found to be 92 per cent (Lye *et al.,* 1976).

Patients and methods

Eleven male and 11 female patients were investigated in this study. Clinically, the patients' cardiac condition was stable and antiheart failure treatment had been unchanged for a period of at least two months before our measurements. All patients were free from oedema at the time of study. Eighteen patients were taking both diuretics and digoxin, three of the 18 were taking thiazide diuretics, while the remainder were taking frusemide (40 to 80 mg); two patients were taking frusemide only; one patient was taking digoxin only, and one patient was not on specific antiheart failure treatment. All patients taking diuretics were also given potassium supplements (7·7 to 48·4 mmol/24 h). Details of the patients studied are given in Table 1.

Table 1 *Details of patients studied*

	Men	*Women*
Age (y)	74 ±6 (67 – 85)	76 ±5 (68 – 84)
Height (cm)	170 ±6 (162 – 182)	150 ±5 (141 – 157)
Weight (kg)	66 ±8 (54 – 86)	51 ±10 (34 – 69)
Fat free mass* (kg)	52 ±6 (45 – 66)	35 ±5 (26 – 43)

Mean ±1 SD.
(Range)
*Fat free mass from skinfold thickness.

Whole body potassium was measured using a Nuclear Enterprises shadow shield monitor to detect the naturally occurring 1·47 MeV gamma rays emitted by ^{40}K. The detectors are four NaI (Tl) crystals, each 152 × 102 mm, two placed above and two placed below the motorised couch. The patient lay supine on the couch which then passed between the detectors, making a complete pass in both directions and the counts were accumulated for a total time of 45 minutes. Each patient was individually calibrated to take account of the attenuation of the gamma rays within the body, using the following method. The patient received an oral dose of 25 μCi of nuclide ^{42}K in the form of the chloride (Radio-chemical Centre, PES. 1P). After 24 hours it was assumed that the geometrical distribution of the ^{42}K was not significantly different from that of the natural ^{40}K. The patient was scanned again for eight minutes and the total counts accumulated. All urine passed during the 24 hours was collected and also counted. This count was compared with a standard comprising 10 per cent of the patient dose in the same volume as the urine sample so that the proportion of the administered dose excreted during the 24 hours could be determined. A phantom consisting of a five litre plastic bottle containing a dose of ^{42}K identical to that administered to the patient was counted for 100 seconds. A second phantom containing a known quantity of natural potassium (Analar KCl) was counted for 800 seconds. Each count was corrected by subtracting a background count measured under the same conditions as the corresponding patient or sample count. All ^{42}K counts were corrected for radioactive decay ($t\frac{1}{2} = 12{\cdot}45$ h) and the patient ^{42}K count was corrected to the count which would have been obtained if all the dose had been retained. Then:

$$\text{WBK mmol} = \text{Pt } {}^{40}\text{K count} \times \frac{\text{phantom K mmol}}{{}^{40}\text{K phantom count}} \times \frac{{}^{42}\text{K phantom count}}{\text{Pt } {}^{42}\text{K count}}$$

The coefficient of variation, which is inversely related to the patient ^{40}K count, of the results obtained by this technique with the present apparatus had a mean value of 4·6 per cent, with a range of 3·2 to 6·7 per cent. We believe that the direct calibration method is more accurate than calculation of a calibration factor based on height and weight (Boddy *et al.,* 1972a).

Total exchangeable potassium was measured concurrently with the whole body potassium and made use of the fact that the patient had already received a dose of ^{42}K. A urine sample was preferred to a plasma sample because of the higher potassium concentration in urine (Surveyor and Hughes, 1968); the associated higher count rate improves the accuracy of the assay. The volume was measured accurately and then the sample was counted on a single crystal of the monitor. A minimum of 2000 counts was acquired. A standard containing 10 per cent of the original dose in the same volume was also counted. All counts were corrected for background and radioactive decay. The 24-hour excreted proportion obtained in the whole body potassium measurement was used to correct the spot urine count. The concentration of potassium in the spot sample was measured by flame emission spectrophotometry using a Pye-Unicam SP 192 atomic absorption spectrophotometer. Then:

$$\text{TeK}_{24}\ \text{mmol} = \text{K content of spot urine} \times \frac{\text{Standard count} \times 10}{\text{Spot urine count}}$$

The urine collection was continued up to 48 ± 2 hours from giving the oral dose at which time a further spot urine sample was taken. TeK_{48} was estimated from this sample in an identical manner. The coefficient of variation of the results obtained by this technique had a mean value of 2·3 per cent, with a range of 0·6 to 5·0 per cent in the case of TeK_{24}, and a mean value of 5·4 per cent, with a range of 1·9 to 14·8 per cent in the case of TeK_{48}. The reason for the greater coefficient of variation for the 48-hour estimate is that, because of radioactive decay, the background count forms a higher proportion of the total count.

The patients were all in hospital at the time of the study and the urine collections were supervised by a research nurse. Patients with incontinence or intermittent confusion were excluded. We are therefore satisfied that most urine collections were complete. In the known cases of incomplete collection, an average value of 96·3 per cent retention was assumed.

Results

The data obtained from the 22 patients are shown in Table 2. The mean whole body potassium of all patients was 2360 ± 640 mmol and ranged from 1350 to 3640 mmol. The ratio of total exchangeable potassium to whole body potassium had a mean value of 77 ± 13 per cent with a range of 32 to 100 per cent at 24 hours and 85 ± 10 per cent with a range of 66 to 106 per cent at 48 hours.

In eight of the 11 men and nine of the 11 women, TeK_{48} was higher than TeK_{24}. In one of the men there was no change in total exchangeable potassium and in two patients of each sex, TeK_{48} was actually lower than TeK_{24}. However, the mean change in total exchangeable potassium shows an increase from 24 to 48 hours for each sex. The pooled data for both sexes show that the mean increase in total exchangeable potassium is 170 ± 310 mmol. Similarly, the mean increase in the ratio of total exchangeable potassium to whole body potassium is 8 ± 14 per cent. In both cases the increase is significant ($t = 2{\cdot}6$, $P < 0{\cdot}01$). TeK_{24} and TeK_{48} are plotted against whole body potassium in the Fig. There is a higher correlation ($r = 0{\cdot}94$) between TeK_{48} and whole body potassium than between TeK_{24} and whole body potassium ($r = 0{\cdot}86$).

A number of patients, not unexpectedly in view of their chronic cardiac failure, had evidence of impaired renal function. The mean blood urea was 8 ± 5 mmol/l, with a range of 5 to 23 mmol/l. There were five patients (three women) whose blood urea was 10 mmol/l or more. The mean creatinine clearance was 56 ± 37 ml/min with a

Table 2 *Individual values of whole body potassium (WBK), exchangeable potassium measured at 24 hours (TeK_{24}) and at 48 hours (TeK_{48}), and derived variables*

	WBK (mmol)	*TeK_{24} (mmol)*	*TeK_{48} (mmol)*	*ΔTeK (mmol)*	*TeK_{24}/ WBK* (%)	*TeK_{48}/ WBK* (%)	*ΔTeK WBK* (%)
Men	2060	1660	1360	−300	81	66	−15
	2860	2360	2500	140	83	87	4
	2840	2080	2220	140	73	78	5
	2350	750	1640	880	32	70	38
	3330	2670	2830	165	80	85	5
	2510	1530	2120	590	61	84	13
	3240	2350	2620	280	73	81	8
	2880	2890	2450	−440	100	85	−15
	3120	2640	2640	0	85	85	0
	2520	2000	2270	260	80	90	10
	3640	2940	3500	560	81	96	15
Mean	2850	2170	2380	210	75	83	7
SD	470	660	570	380	17	9	15
Women	1350	1040	1140	100	77	85	8
	1810	1470	1560	88	81	86	5
	1730	1230	1420	190	71	83	12
	1600	1150	1330	180	72	83	11
	1660	1300	1720	420	79	104	25
	2010	1510	1840	330	75	91	16
	1730	1540	1830	290	89	106	17
	2590	1950	2360	410	76	91	15
	2200	1910	1680	−230	87	76	−11
	2150	1490	1600	110	69	74	5
	1810	1620	1310	−310	90	73	−17
Mean	1880	1470	1620	140	79	87	8
SD	340	290	330	240	7	11	12
Pooled mean	2360	1820	2000	170	77	84	8
SD	640	610	600	310	13	10	14

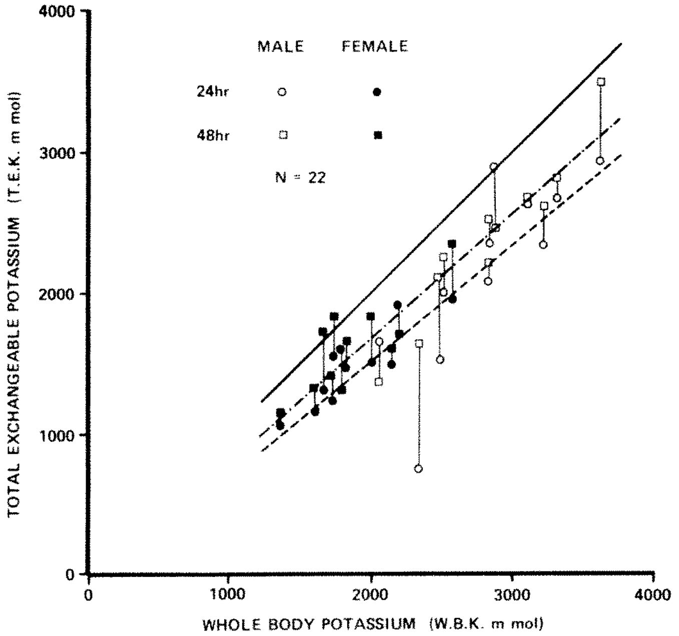

Fig. *Relation of whole body potassium (WBK) to total exchangeable potassium measured at 24 hours ----- (TeK_{24}), and at 48 hours —·—· (TeK_{48}).*

range from 7 to 116 ml/min. Six patients had a creatinine clearance below 20 ml/min and two patients had values below 10 ml/min. The ratios TeK_{24}/WBK and TeK_{48}/WBK did not significantly correlate ($P > 0{\cdot}05$) with the blood urea ($r = 0{\cdot}03$ and 0·38, respectively) or with the creatinine clearance ($r = 0{\cdot}01$ and 0·27, respectively).

Discussion

Our results give a value of 77 per cent at 24 hours and 84 per cent at 48 hours for the ratio of total exchangeable potassium to whole body potassium, compared with an average normal value of 93 per cent reported previously. The only methodological factor which could affect the results was the completeness of the 24-hour urine collections. However, an incomplete urine collection would lead to an over-estimate of both total exchangeable potassium and whole body potassium and would, therefore, not affect the ratio. It is possible that either the proportion of whole body potassium which is exchangeable is reduced in patients with cardiac failure, or that a value within the normal range would have been obtained had measurements been extended beyond 48 hours. Because we have only two measurements for each patient, it is not possible to distinguish between these possibilities.

Boddy *et al.* (1972b) found that the ratio of total exchangeable potassium to whole body potassium was significantly reduced in patients with chronic renal failure, that is patients in whom creatinine clearance is less than 10 ml/min. However, the present study shows no correlation between completeness of equilibration at 24 or 48 hours and indices of renal function. It is perhaps interesting to note that the patients with chronic bronchitis studied by Boddy *et al.* (1978) had all experienced one or more episodes of fluid retention, but at the time of study they were, as were our patients, free from oedema.

The fact that total exchangeable potassium increased significantly during the second 24-hour period leads us to believe that equilibration times are increased in the present group of subjects and confirms the findings of earlier reports on patients with cardiac failure. Where body potassium has been estimated from measurements of total exchangeable potassium, it has been suggested that body potassium is significantly reduced (Davidson and Gillebrand, 1973; Nicholls *et al.*, 1976; *British Medical Journal*, 1977). However, where whole body potassium has been measured by whole body counting, little or no deficit has been found (Delwaide and Rorive, 1973; Davidson *et al.*, 1976; Lawson *et al.*, 1976). The present study confirms that, for patients with cardiac failure, the quantification of the degree of potassium depletion by measuring total exchangeable potassium may well exaggerate the degree of depletion, and caution should be exercised in basing any treatment regimen on such tests.

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Effects of amiodarone on sinus node in man

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SUMMARY The effects of amiodarone on the sinuatrial node were studied in 24 patients after an intravenous injection of the drug (5 mg/kg). Sinuatrial function was assessed by rapid atrial pacing and premature atrial stimulation. Sinus cycle length did not change significantly, but the corrected sinus node recovery time was prolonged. While there was no significant change in sinuatrial conduction time, prolongation of the non-reset zone in 14 cases, as well as the abolition of the plateau in 2/24 patients, suggested that conduction of the atrial responses to the sinus node might have been depressed.

Amiodarone was initially used as an antianginal drug (Vastesaeger *et al.*, 1967), but was later found to possess antiarrhythmic properties. Many clinical studies have confirmed the efficacy of this drug against both supraventricular and ventricular arrhythmias (Coumel and Bouvrain, 1973; Fauchier *et al.*, 1973; Rosenbaum *et al.*, 1976). Amiodarone was found especially effective in controlling refractory atrial arrhythmias associated with the Wolff-Parkinson-White syndrome (Rosenbaum *et al.*, 1974). Though amiodarone was increasingly used for clinical purposes, its therapeutic advantages were somewhat counteracted by various side-effects such as cutaneous disorders (Wanet *et al.*, 1971; Morand *et al.*, 1972), corneal deposits (Francois, 1968; Verin *et al.*, 1971), and hyperthyroidism or hypothyroidism because of the presence of iodine in the compound (Barrillon and Himbert, 1971; Grand, 1975; Pritchard *et al.*, 1975). As severe bradycardia was also observed (Van Schepdael and Solvay, 1970), we carried out the present study so as to elucidate the effects of amiodarone on sinus node function.

Patients and methods

Twenty-four patients were studied, 13 men and 11 women, aged from 51 to 77 years (mean: 64). None of the patients was suffering from sinuatrial disorder as defined by severe bradycardia of less than 50/min or episodes of sinus arrest. However, during the study, two subjects exhibited heart rates of 52 and 55/min, respectively, so that some degree of sinuatrial involvement could not be excluded. In two others, sinus tachycardia was noted, presumably caused by anxiety. Atrioventricular conduction abnormalities were present in 16 cases (long PR interval in one and bundle-branch block or fascicular block in 15). Despite theoretical reservations, these patients were included in the study, since there was no evidence that they would be more prone to sinuatrial alteration than the others.

Electrophysiological studies were performed in the postabsorptive, non-sedated state, after informed consent had been obtained. Of the 24 patients, 22 complained of syncope or dizziness (Table). The remaining two (cases 1 and 21) had latent electrocardiographic abnormalities. All medication with cardiac effects was stopped at least eight days before the study. The procedure was similar to that previously reported (Touboul *et al.*, 1975). Four electrode catheters were introduced percutaneously through the right and left femoral veins. Of these, a tripolar catheter was used for recording His bundle activity according to Scherlag (Scherlag *et al.*, 1969), and another was positioned at the apex of the right ventricle for electrical pacing. The remaining two catheters were inserted into the right atrium. A bipolar electrogram was recorded at the junction of the superior vena cava and the external border of the atrium. In addition, atrial stimulation was performed in the region of the sinus node. A modular programmable stimulator was used[1]. Electric impulses were rectangular of 1·5 ms duration, and were delivered at twice diastolic threshold intensity. We used an eight channel direct ink jet recorder[2]. Paper speed during the study was 100 mm/s. Intracardiac electrograms were transmitted through amplifiers. The potentials in the His

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[2] Elema Schönander, Sweden.

Table *Data on patients*

Case no.	*Age (y)*	*Sex*	*Clinical data*	*ECG*	*Sinus cycle length (ms)*		*CSNRT (ms)*		*EASACT*	
					Before	*After*	*Before*	*After*	*Before*	*After*
1	65	M	No symptom	RBBB	875	840	290	350	210	210
2	55	M	Syncope	RBBB	580	550	140	150	120	150
3	51	F	Hypertension, AHD, syncope	N	950	965	250	230	110	85
4	64	M	Hypertension, syncope	LBBB	800	850	370	300	140	130
5	66	F	Syncope	N	1160	1000	60	170	110	180
6	77	F	Hypertension, AHD, syncope	N	1100	1050	450	520	150	200
7	61	M	Diabetes, AHD, palpitation, syncope	LBBB	660	640	170	280	210	210
8	72	F	Hypertension, syncope	ILBBB	930	870	260	470	220	230
9	71	F	Syncope	N	730	680	390	230	270	No plateau zone
10	63	F	Syncope	N	700	730	240	200	140	150
11	72	M	AHD, dizziness	OMI	900	980	270	400	80	130
12	58	M	PAD, syncope	N	930	870	190	410	220	195
13	59	M	Syncope	N	900	870	280	370	250	300
14	70	M	PAD, syncope	RBBB LAH	830	920	370	580	340	320
15	68	F	Syncope	N	590	625	190	140	130	135
16	56	M	Syncope	RBBB LAH	830	750	150	260	130	200
17	70	F	Palpitation, syncope	N	900	950	380	650	260	230
18	76	F	Hypertension, syncope	RBBB LAH	830	980	290	320	250	210
19	73	F	Hypertension, syncope	N	800	810	370	300	300	220
20	58	M	Syncope	IRBBB LAH	800	800	230	250	200	160
21	75	F	RLD	LBBB	710	810	280	290	190	160
22	52	M	Hypertension, syncope	VPB	850	880	360	350	230	200
23	57	M	Dizziness	1st/degree AV block	650	680	270	470	250	No plateau zone
24	70	M	AHD, syncope	LBBB	950	880	310	340	150	190

Abbreviations: N, normal; AHD, atherosclerotic heart disease; PAD, peripheral arterial disease; RLD, restrictive lung disease; RBBB, right bundle-branch block; LBBB, left bundle-branch block; ILBBB, incomplete left bundle-branch block; LAH, left anterior hemiblock; VPB, ventricular premature beats; OMI, old myocardial infarction; CSNRT, corrected sinus node recovery time; EASACT, estimated atrio-sinuatrial conduction time.

bundle lead were filtered (recording frequencies: 50 to 700 Hz). Five external leads were recorded simultaneously: I, II, III, V1, and V6. Either lead I or II, as well as one selected intracardiac lead, were visualised on an oscilloscope and all data were stored on magnetic tape.

Sinus node function was assessed using two methods. Sinus node recovery time was measured by rapid atrial pacing at successive rates of 110, 130, 150, and 170 a minute (Mandel *et al.*, 1971). Each rate was maintained for 30 s. The pause between the pacing sequences was about one minute. Sinus node recovery time corresponds to the interval between the last paced P wave and the first sinus P wave. In this study we took account of the two relevant electrograms recorded in the intra-atrial lead. Times measured were corrected as a function of basic sinus cycle length, in accordance with the formula of Narula *et al.* (1972):

Corrected sinus node recovery time = sinus node recovery interval – sinus cycle length.

The sinus cycle length was an average value, calculated from the five sinus cycles preceding each pacing sequence. Whatever the pacing rate, only the longest corrected sinus node recovery time was taken into account.

Sinuatrial conduction time was determined according to the technique of Strauss *et al.* (1973). Premature atrial depolarisation was induced during sinus rhythm at every eighth or tenth beat. The coupling interval was long at first but was subsequently reduced by periods of 20 ms until the effective refractory period of the right atrium was reached. A curve was constructed by plotting the A1-A2 coupling intervals along the abscissa and the A2-A3 return cycles along the ordinate. Normally, this curve comprises two parts. At long coupling intervals, an ascending limb called the non-reset zone (zone 1) follows the compensatory line. The return cycles then become constant, and form a horizontal segment or plateau zone, as atrial depolarisations reach and discharge the pacemaker cells (as noted in isolated preparations). Sinus node activity was then reset and, after a new cycle, induced an earlier P wave (Miller and Strauss, 1974). Consequently the relevant A2-A3 interval, as determined in clinical studies, is presumed to include a sinus cycle and, in addition, the conduction time taken by the retrograde impulse to reach the sinus node, as well as the sinuatrial conduction time of the sinus beat after the pause, hence the following formula:

$$\text{Sinuatrial conduction time} = \frac{\text{A2-A3 interval} - \text{sinus cycle length}}{2}$$

In this study, we used the estimated atrio-sinuatrial conduction time, as follows:

$$\text{Estimated atrio-sinuatrial conduction time} = \text{A2-A3 interval} - \text{sinus cycle}$$

The A2-A3 intervals were measured from the first third of the plateau. The sinus cycle length was an average value, calculated from all the cycles immediately preceding the premature atrial stimulation. The graphs were examined independently by two physicians from our laboratory and satisfactory concordance was obtained.

We carried out repeated studies of sinus node function after slow intravenous administration (five minutes) of 5 mg/kg amiodarone hydrochloride. Premature atrial stimulation and overdrive tests were carried out successively. The fresh evaluation was started five minutes after termination of the amiodarone injection. Statistical analysis of the results was made using Student's t test for paired data.

Results

The data on sinus node function are given in the Table.

After amiodarone administration, sinus cycle length increased in 12 cases by a mean of 55 ms, decreased in 11 by 58 ms, and remained unchanged in one (NS).

Corrected sinus node recovery time was longer in 17 subjects (mean: 110 ms) and shorter in the remaining seven (mean: 60 ms). These changes are statistically significant ($P < 0{\cdot}02$).

Estimated atrio-sinuatrial conduction time was determined before and after amiodarone in 22 patients. It lengthened in 10 cases by a mean of 38 ms, diminished in 10 (mean 33 ms), and did not change in two (NS). In the remaining two patients, the plateau zone was abolished after amiodarone administration (Fig. 1).

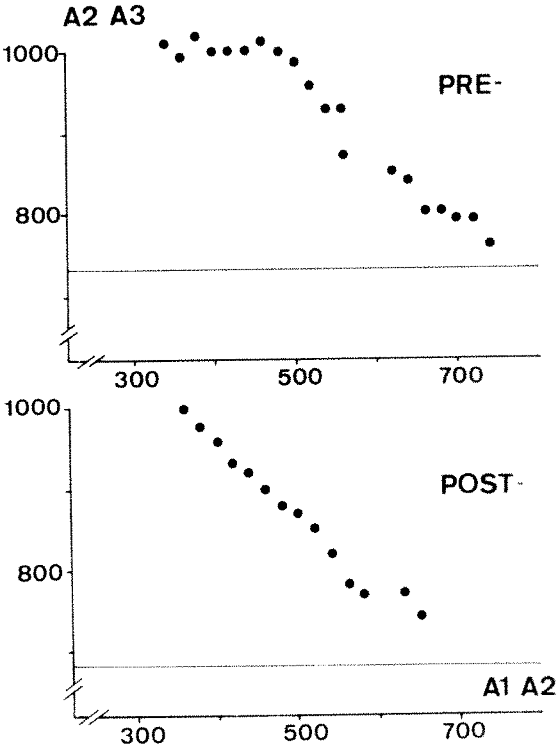

Fig. 1 *Suppression of the plateau zone after amiodarone. Coupling intervals (A1-A2) are in abscissa, return cycles (A2-A3) in ordinate. Figures are in milliseconds. In the basal state (Pre-), both phases I and II are clearly visible. After amiodarone (Post-), only zone I is maintained. The suppression of the plateau suggests that the atrial depolarisations can no longer reach the pacemaker cells. The line parallel to the abscissa corresponds to the mean sinus cycle length.*

In addition, certain changes in the A1A2/A2A3 curve occurred after injection of the drug. Thus, the duration of the non-reset zone, expressed as a percentage of the mean sinus cycle, increased in 14/22 patients by 11 per cent, decreased in seven by 2 per cent, and did not change in one ($P < 0{\cdot}005$). Sometimes a smooth transition developed between the compensatory line and the plateau (Fig. 2). After early atrial depolarisations (coupling interval of less than 50 per cent of the sinus cycle), the return cycles showed a gradual increase in 10 patients, causing the latter part of the plateau to ascend (Fig. 3).

There were no untoward effects after the injection of amiodarone.

Discussion

The electrophysiological properties of amiodarone have been defined in previous studies. In isolated rabbit heart preparations, amiodarone prolonged the duration of the action potential in atrial and ventricular muscle without changing the resting potential

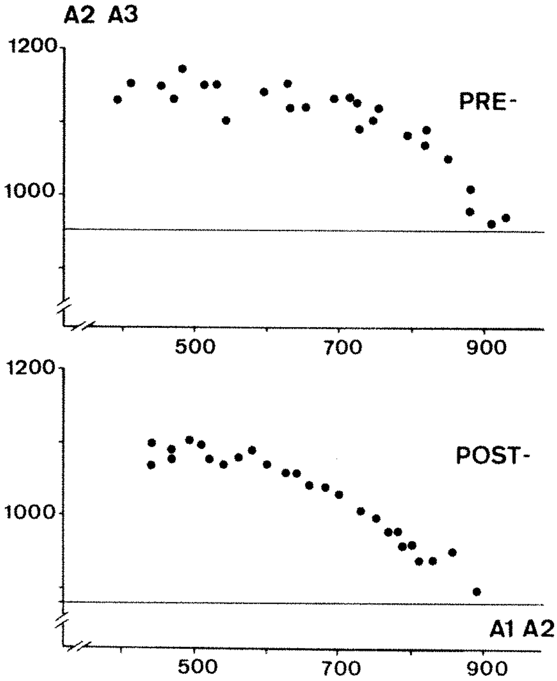

Fig. 2 *Effect of amiodarone on sinuatrial conduction time. Estimated atrio-sinuatrial conduction time before amiodarone is 150 ms (Pre-). After amiodarone, it increases to 190 ms (Post-). In addition, segment I is prolonged and moves down to below compensatory line before joining the plateau (see explanation in the text).*

or the maximum rate of rise (Singh and Vaughan Williams, 1970). In man, atrioventricular nodal conduction was depressed after intravenous injection of 5 mg/kg, whereas the His-Purkinje conduction time remained unchanged. The refractory periods of the atrioventricular conducting tissue (AV node and His-Purkinje system) and of the atrial and ventricular myocardium increased (Cabasson *et al.*, 1976; Touboul *et al.*, 1976a). The drug also lengthened the effective refractory period of the accessory pathway in patients with the Wolff-Parkinson-White syndrome (Touboul *et al.*, 1976b); Wellens *et al.*, 1976).

As regards the effect of amiodarone on sinuatrial activity, slowing of the sinus node discharge was reported in the anaesthetised dog even after pretreatment with propranolol and atropine (Charlier, 1970). In rabbit sinus node preparations, amiodarone prolonged action potential duration and reduced the slope of spontaneous diastolic depolarisation (Goupil and Lenfant, 1976). Furthermore, recent studies using epicardial recording of sinus node activity have suggested that amiodarone might induce sinuatrial block (Castillo-Fenoy *et al.*, 1978).

In man our results show an increase in sinus node recovery time after amiodarone administration. Surprisingly, sinus node cycle length did not alter significantly, a finding which contrasts with the well-known possibility that clinical use of the drug can induce bradycardia. Several checks of our batch of amiodarone by the manufacturer failed to disclose any abnormality which might have accounted for this finding. An explanation was also sought in the mode of intravenous administration, despite the fact that a slowing down of the sinus rate has been reported in similar studies (Touboul *et al.*, 1976a). In this connection, the part played by autonomic changes should be mentioned, with special reference to the opposite effects of vasodilatation and partial adrenergic blockade on cycle length. In addition, it is conceivable that, after the doses of amiodarone used here, myocardial depression could have occurred, favoured in some of our patients by latent abnormalities (Sicart *et al.*, 1977). The sympathetic

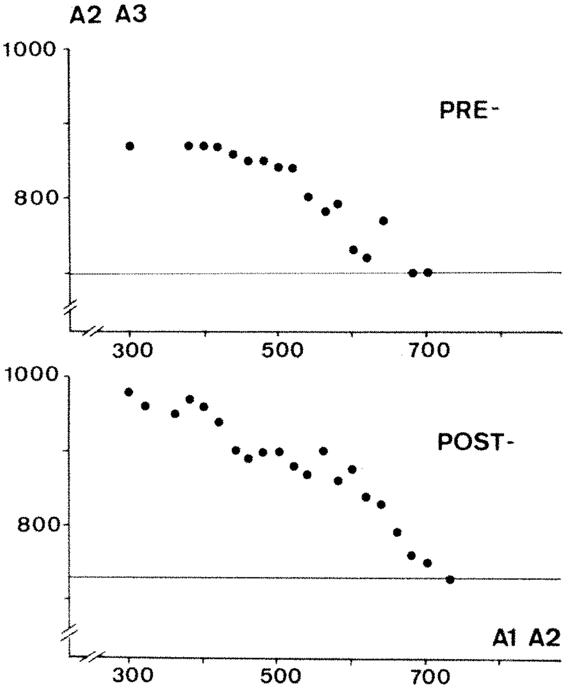

Fig. 3 *Effect of amiodarone on the sinus node response after early premature atrial stimulation. Estimated atrio-sinuatrial conduction time measured at the first third of the plateau does not change after amiodarone. On the other hand, the terminal part of the plateau moves upwards as a result of return cycle lengthening (see explanation in the text).*

stimulation thus induced would have counteracted the direct effect of amiodarone on the sinus node.

It should be stressed that during premature atrial stimulation, abolition of the plateau zone was noted in two cases, after amiodarone. The drug thus occasionally suppressed retrograde conduction to the pacemaker cells. This might be the result of the slowing of sinuatrial transmission and the resulting prolongation of the refractory state within the junction area. Even in the remaining patients, depressed retrograde conduction of the atrial depolarisations was shown, despite the absence of significant effects on sinuatrial conduction time. The increase in the duration of zone I therefore meant that late atrial reponses reaching the sinus node in the control state might be blocked within the junction after amiodarone. However, these responses were likely to penetrate still deeply into the sinus node area and to die out in the vicinity of the pacemaker cells. According to studies on the rabbit sinus node by Miller and Strauss (1974), electrotonic shortening of the action potential duration of the pacemaker cells might ensue, making the next discharge occur earlier and therefore reducing the A2-A3 interval. This would explain the possible lowering of the terminal part of segment I below the compensatory line, resulting in a smooth transition between both zones.

As for the lengthening of the return cycles observed after amiodarone injection at short coupling intervals, one of two mechanisms may be responsible: either further slowing of the early atrial responses, a result of the prolongation of the relative refractory period within the sinuatrial junction or the atrium itself, or depressed automaticity of the sinuatrial cells after sufficiently premature stimulation (Bonke *et al.*, 1971).

The present data thus support the view that amiodarone impairs sinus node function. The results of premature atrial stimulation suggest that conduction within the sinuatrial junction can be depressed by the drug. Such changes shed light on the possible mechanisms of side-effects in man. In this respect, further studies are required to assess the action of amiodarone in patients with the sick sinus syndrome. A specific factor in the antiarrhythmic activity of amiodarone appears to be its accumulation in the tissues (Rosenbaum *et al.*, 1976); electrophysiological changes are not necessarily the same after prolonged oral treatment as after intravenous injection. These limitations must be kept in mind for proper appraisal of our data.

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Arterial counterpulsation in continuing myocardial ischaemia after acute myocardial infarction

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SUMMARY Twenty-six patients underwent arterial counterpulsation for refractory heart failure without shock complicating acute myocardial infarction. Patients were divided into a group of 12 with continuing myocardial ischaemia, evidenced by anginal pain associated with abnormal ST segment elevation, and a group of 14 without continuing ischaemia. Clinical features (apart from pain) and prognostic indices were similar in the two groups when counterpulsation was started but short- and long-term results were different.

Hospital survival was 92 per cent (11/12) and 43 per cent (6/14), respectively, in the groups with and without ischaemia and four-year survival was 73 per cent and 7 per cent. Counterpulsation is of greatest value in acute infarction when used to relieve myocardial ischaemia.

While arterial counterpulsation has been used widely and increasingly over the past eight years in patients with acute coronary artery disease, there is still no consensus as to how it can be applied most effectively. Apart from use in surgical patients, the principal application has been at the two extreme ends of the spectrum of acute infarction—in patients with cardiogenic shock on the one hand (Dunkman *et al.*, 1972; Scheidt *et al.*, 1973; Jackson *et al.*, 1977) and in patients with threatening infarction or coronary insufficiency on the other (Mundth, 1976; Leinbach *et al.*, 1978). Despite the use of counterpulsation, mortality rate has remained high in cardiogenic shock and low in coronary insufficiency. No controlled trials have been reported and it is disputed that counterpulsation offers any advantage over conventional treatment in either condition (Forrester *et al.*, 1976; Kuhn, 1976; O'Rourke, 1977).

Counterpulsation has been shown in animals (Goldfarb, 1969; Powell *et al.*, 1970; Maroko *et al.*, 1972) and in man (Mueller *et al.*, 1971; Maroko *et al.*, 1972) to provide substantial relief of myocardial ischaemia, through reduction in ventricular afterload and increase in myocardial perfusion. The animal experimental studies have confirmed that counterpulsation can reduce infarct size and improve survival when initiated at a time when reversible ischaemia is still in evidence.

It has been suggested (Scheidt *et al.*, 1973; O'Rourke *et al.*, 1975) that indifferent results of counterpulsation in patients with acute infarction are the result of it being initiated so late after onset of symptoms, that myocardial ischaemic damage has become irreversible. In order to test this theory, we reviewed results of patients undergoing counterpulsation for refractory heart failure without shock after acute infarction. Patients in cardiogenic shock were excluded because clouded consciousness in the majority prevented accurate interpretation of chest pain; in addition we wished to eliminate the haemodynamic and metabolic effects of shock itself (Page *et al.*, 1971; Mueller and Ayres, 1974).

Patients

During the six-year period to December 1977, 26 patients with acute infarction underwent counterpulsation for refractory heart failure without shock, using the Avco intra-aortic balloon system. During the same period, 86 patients with cardiogenic shock were treated with counterpulsation.

All 26 patients had clinical, electrocardiographic, and enzymatic evidence of acute infarction by WHO criteria. All had severe and persistent cardiac failure despite conventional medical treatment.

Twelve patients were considered to have continuing ischaemia on the basis of persistent anginal pain unresponsive to glyceryl trinitrate, together with abnormal ST segment elevation in electrocardiographic leads showing the infarct pattern: these comprised group 1. The other 14 patients did

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not have continuing ischaemic chest pain at the time counterpulsation was started: these comprised group 2.

Clinical features of patients in the two groups were similar (Table).

Prognostic indices (Peel *et al.,* 1962; Norris *et al.,* 1969) predicted survival rates less than 50 per cent in both groups. The only significant difference was the time between onset of symptoms and introduction of counterpulsation, which averaged 26 hours (median 19 hours) in group 1 and 155 hours (median 57 hours) in group 2.

Patients were monitored through the period of counterpulsation with direct measurement of pulmonary artery and brachial or radial artery pressure. Counterpulsation was continued for one to 15 (mean 7·5) days, the duration being determined by death or the time required for maximal sustained improvement (O'Rourke *et al.,* 1979). One patient in group 1 underwent coronary artery bypass grafting when anginal pain recurred after termination of counterpulsation. Three patients in group 2 underwent coronary artery bypass grafting during the period of counterpulsation because of continuing heart failure or arrhythmias; all these patients died in hospital. One patient in group 2 had repair of acute ventricular aneurysm; this patient is still living and the only one in group 2 not to be disabled subsequently.

Table *Patients with severe refractory heart failure complicating acute myocardial infarction*

	Continuing ischaemia (group 1)	*No ischaemia (group 2)*
Number	12	14
Previous infarction	4	4
Age (y)	51	55
Prognostic indices		
Peel	$\overline{19\cdot5}$	$\overline{20\cdot5}$
Norris	$\overline{9\cdot8}$	$\overline{10\cdot8}$
Peak CK level (IU/l)*	1776 ± 1309	1858 ± 1314
Onset symptoms→CP (hours)		
Median	19	57
Range	5–72	8–456
Arterial pressure (mmHg)		
(before CP)	$\overline{116/72}$	$\overline{106/76}$
(after 24 hours CP)	$\overline{75/109}$	$\overline{79/103}$
(at termination of CP)	$\overline{108/72}$	$\overline{102/72}$
Heart rate		
(before CP)	$\overline{119}$ ± 13SD	$\overline{117}$ ± 18
(after 24 hours CP)	$\overline{101}$ ± 14	$\overline{107}$ ± 18
(at termination of CP)	$\overline{81}$ ± 10	$\overline{101}$ ± 9
Pulmonary artery pressure (mmHg)		
(before CP)	$\overline{33}$ ± 7	$\overline{31}$ ± 8
(after 24 hours CP)	$\overline{18}$ ± 5	$\overline{20}$ ± 7
(at termination of CP)	$\overline{12}$ ± 3	$\overline{16}$ ± 4
Duration of CP (days)	$\overline{8\cdot9}$	$\overline{6\cdot3}$

*Normal upper level of normal 40 IU/l.
CP, counterpulsation.

All hospital survivors were reviewed periodically after discharge, with interview and examination performed by one of us; functional status was assessed according to the New York Heart Association criteria. Follow-up period was one to 56 (mean 33) months. No patient was lost to follow-up.

Results

While all patients showed improvement with initiation of counterpulsation, this was more prompt, more distinct, and more sustained in the patients with continuing ischaemia. The effect on ischaemic pain was quite dramatic, this being abolished within minutes in 11 patients and within 12 hours in the other. Cardiac failure was eased in all patients, but the most obvious benefit (reflected in change of pulmonary artery pressure and heart rate (Table)) was seen in group 1 patients.

Of the 12 patients in group 1 there was only one hospital death—from low output cardiac failure 27 days after termination of counterpulsation. Of the 14 patients in group 2 there were eight hospital deaths—three from late ventricular fibrillation and five from cardiac failure. Difference in hospital survival (92% in group 1, 43% in group 2) was statistically significant ($P < 0{\cdot}01$).

Two of the 11 hospital survivors in group 1 and four of the six in group 2 died during the follow-up period. One died suddenly, two after reinfarction, and three from chronic cardiac failure. Survival rate at four years (Fig.) was 73 per cent in group 1 and 7 per cent in group 2 ($P < 0{\cdot}005$).

Of the nine patients in group 1 who were alive at follow-up, six were in NYHA functional class 1 or 2. There were only two survivors at follow-up in group 2, and only one in functional class 1 or 2; this patient had undergone repair of ventricular aneurysm in association with counterpulsation.

Discussion

The patients presented here had a poor prognosis with continuation of conventional treatment. The group without evidence of continuing ischaemia had a hospital mortality close to that predicted from prognostic indices (57% observed *cf* 50% predicted by Peel and Norris indices), and high late mortality after hospital discharge. Counterpulsation does not appear to have helped these patients. In contrast, counterpulsation appears to have substantially

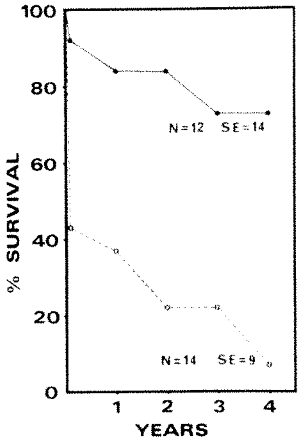

Fig. *Life table: unbroken line: patients with continuing myocardial ischaemia at initiation of counterpulsation (group 1), broken line: patients without continuing myocardial ischaemia at initiation of counterpulsation (group 2). Significance at four years, $P < 0{\cdot}005$.*

improved the outlook of patients with persistent myocardial ischaemia; in these, hospital mortality, late mortality, and late morbidity were considerably better than in the group whose clinical features were essentially similar, except for the absence of myocardial ischaemia. The fact that improvement in morbidity and mortality was associated with prompt relief of anginal pain after counterpulsation was started suggests that such improvement resulted directly from relief of myocardial ischaemia and preservation of reversibly damaged muscle. This is what one might expect from theoretical considerations and animal experimental studies (Goldfarb, 1969; Powell *et al.,* 1970; Mueller *et al.,* 1971; Maroko *et al.,* 1972).

Patients with continuing myocardial ischaemia underwent counterpulsation much earlier than those without continuing ischaemia, the median delay after onset of symptoms being 19 *cf* 57 hours. It is possible that this factor alone may have been more important than the presence of ischaemia in determining favourable outcome though this seems unlikely. In group 2, delay before onset of symptoms and counterpulsation was similar in those who died in hospital (median 53 hours) and in those who survived (median 61 hours). Further, in group 1, the one hospital death and the two late deaths occurred in patients undergoing counterpulsation early (seven hours, five hours, and 18 hours, respectively) after the onset of symptoms. Certainly results were very poor in patients who underwent counterpulsation more than four days after the onset of symptoms. (Of four such patients, there was only one survivor—and this patient required excision of acute ventricular aneurysm.) It is probable that myocardial ischaemia and delay after onset of symptoms are not independent determinants of survival in relation to use of counterpulsation, but that myocardial ischaemia is more likely to be present early rather that late after onset of symptoms. In other words, counterpulsation was most effective when applied early after onset of symptoms because there was usually more ischaemia and more reversible damage present at this time.

Results presented here support the view that counterpulsation is of greatest value in acute infarction when used early after onset of symptoms to relieve continuing myocardial ischaemia. We are currently testing this hypothesis in a ramdomised controlled trial.

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Carotid sinus hypersensitivity in patients presenting with syncope

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SUMMARY In 23 patients (ages 44 to 81) presenting with syncope, vertigo, or transient amnesia, carotid sinus massage produced a significant bradycardia in association with symptoms. The 10 most severely symptomatic patients were studied electrophysiologically, including measurement of intracardiac conduction times and corrected sinus node recovery times, as well as with carotid sinus massage before and after atropine. The only detectable abnormality in five of this group was asystole produced by carotid sinus massage; the other five had, in addition, evidence of either sinuatrial disease or an intracardiac conduction defect. Cardiac pacing in these 10 patients completely abolished their symptoms. In a control group of 52 asymptomatic patients (ages 36 to 87), an abnormal response to carotid sinus massage was uncommon (2%).

Syncope, vertigo, and transient amnesia are common clinical problems and may result from many different conditions. Recently, it has been recognised that in some patients presenting with these symptoms an underlying arrythmia may be the primary cause (Abdon and Malmcrona, 1975). The carotid sinus syndrome is a rare cause of symptoms in association with transient bradycardias (Weiss and Baker, 1933; Ferris *et al.*, 1935).

In patients presenting with idiopathic syncope, carotid sinus massage may induce severe bradycardia. We report on a study of such a group of patients, in whom intracardiac electrophysiological tests were performed during carotid sinus massage.

Patients and methods

(1) CONTROL GROUP

The response of heart rate to carotid sinus massage was assessed in a control group of 52 men in hospital (ages 36 to 87). They were in sinus rhythm, with no evidence of cardiac or neurological disease and had normal resting electrocardiograms. None had suffered from syncope or disturbance of consciousness or other symptoms related to the central nervous or cardiovascular systems.

(2) SYMPTOMATIC GROUP

Over an 18-month period, 23 patients (15 men, eight women) referred for evaluation of syncope, near syncope, or transient amnesia (Table 1) had an abnormal response to carotid sinus massage, and they have been followed up over a period of 18 months to three years. All patients had a full history taken, clinical examination, and resting electrocardiogram. Carotid sinus massage was performed by the same observer in all cases, with the patient in a semirecumbent position of 45 degrees. Continuous electrocardiographic monitoring was carried out while the carotid sinus was massaged for five seconds unless asystole with symptoms intervened. All drug treatment had been withdrawn for at least 48 hours before this manoeuvre. None had been receiving digitalis or beta-blocking agents before study. An abnormal response was considered to be present if asystole occurred for more than three seconds (Thormann and Schwartz, 1975; Scarpa, 1976).

Intraventricular conduction disturbances were diagnosed from the electrocardiogram, using the criteria of Rosenbaum (1970). Ten severely symptomatic patients were submitted to electrophysiological studies which included measurement of intraventricular conduction times and measurement of corrected sinus node recovery times after atrial pacing at various rates (Narula *et al.*, 1972). Carotid sinus massage was also performed and all measurements were then repeated after the intravenous administration of 1·2 mg atropine.

Results

(1) CONTROL GROUP

In these 52 patients carotid sinus massage produced slowing of the sinus rate. The maximal RR

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Table 1 *Patients with abnormal response to carotid sinus massage; cases 1 to 10 studied electrophysiologically and paced permanently*

Case no.	*Age (y)*	*Symptoms*	*Associated diseases*	*Electrocardiogram*
1	67	Syncope 1 month	Hypertension	Normal
2	73	Syncope 6 months	Nil	Sinus bradycardia/ SA block
3	49	Syncope/amnesia 8 years	Coronary artery disease	Normal
4	52	Syncope/amnesia 3 months	Coronary artery disease	Normal
5	55	Syncope 2 years	Hypertension	Left axis
6	64	Syncope/light-headedness 6 months	Coronary artery disease	Normal
7	69	Syncope/amnesia 2 years	Nil	Normal
8	66	Syncope 1 year	Coronary artery disease; diabetes	Intermittent lt axis SA block
9	71	Amnesia 2 years	Nil	Intermittent LBBB
10	66	Amnesia 10 years	Hypertension	Left axis
11	60	Syncope 30 years	Hypertension	Left axis
12	54	Syncope 18 months	Coronary artery disease	Normal
13	47	Light-headedness	Nil	Normal
14	64	Amnesic episodes 1 year	Nil	Normal
15	67	Syncope/vertigo 1 year	Nil	Normal
16	67	Vertigo	Hypertension	Normal
17	66	Vertigo	Coronary artery disease	Intermittent RBBB
18	82	Syncope 2 years	Hypertension	Normal
19	44	Syncope/vertigo 3 years	Nil	RAD
20	63	Syncope 1 year	Cerebrovascular disease	Intermittent atrial fib
21	74	Syncope 6 months	Cerebrovascular disease	LBBB
22	73	Syncope	Nil	Normal
23	72	Syncope 3 years	Coronary artery disease	Left axis

prolongation obtained, expressed as a percentage of the resting RR interval, was 127 ±30 per cent. In one patient, asystole of 4·6 seconds was produced on one occasion only.

(2) SYMPTOMATIC GROUP

In the 23 symptomatic patients (Table 1), carotid sinus massage produced asystole lasting longer than three seconds in association with cerebral symptoms. The standard electrocardiograms were normal in 12 patients; in the remaining 11, two showed periods of sinuatrial block: one of these patients also had intermittent atrial fibrillation and one had persistent left bundle-branch block.

Electrophysiological investigation of 10 patients (cases 1 to 10, Table 1) showed that five patients with normal resting electrocardiograms had normal sinus node function with conduction times, the only abnormality being an abnormal response to carotid sinus massage which was totally abolished by intravenous atropine.

The two patients (cases 2 and 8) with electrocardiographic signs of sinuatrial block showed evidence of gross sinuatrial node dysfunction with post-pacing asystole for 3 and 5·3 seconds followed by a slow junctional escape rhythm. After intravenous atropine, the junctional escape rhythm was preceded by asystole for 2 and 4·9 seconds, but their abnormal response to carotid sinus massage was totally abolished. Three cases with left axis deviation had prolongation of HV intervals (Table 2).

The 10 patients who underwent electrophysiological tests had cardiac pacemakers implanted; on follow-up (18 months to three years) their symptoms have completely disappeared. The remaining 13 patients (cases 11 to 23), whose symptoms were

Table 2 *Results during electrophysiological study: intervals in milliseconds*

	Before atropine				*After atropine*			
Case no.	*RR*	*HV*	*CSNRT*	*CSM rr*	*RR*	*HV*	*CSNRT*	*CSM rr*
1	850	50	10	4700	720	50	–5	810
2	950	50	5300 JER	9330	660	50	4900 JER	660
3	930	45	180	7950	850	45	160	1130
4	990	55	0	3460	610	55	50	610
5	1005	60	150	3050	910	60	130	920
6	950	55	320	4260	890	55	300	950
7	910	45	35	7850	850	45	55	850
8	1020	35	3050 JER	3100	810	50	2030 JER	820
9	830	75	270	3490	590	75	205	590
10	770	70	50	3150	620	75	10	640

HV, conduction time His-Purkinje system (normal 35 to 55 ms); CSNRT, corrected sinus node recovery time (normal < 525 ms); CSM, carotid sinus massage (normal < 3000 ms); JER, junctional escape rhythm.

mild and infrequent, did not receive pacemakers and their symptoms persisted.

Discussion

Hypersensitivity of the carotid sinus reflex has long been recognised to be associated with spontaneous syncope. The carotid sinus syndrome is a term reserved for symptomatic patients who have an abnormal response to carotid sinus massage (Weiss and Baker, 1933; Ferris *et al.*, 1935). Several investigators have shown that, in an asymptomatic population, a significant number of people will show severe bradycardia on carotid sinus massage (Purks, 1939; Heidorn and McNamara, 1956; Sigler, 1963). The prevalence of an abnormal response appears to vary according to the duration of the pressure of stimulus applied to the carotid sinus. Thus, in 25 per cent of normal subjects, massage for 30 seconds produced asystole, with or without symptoms (Heidorn and McNamara, 1956).

Massage for 12 seconds in patients with ischaemic heart disease often produced severe bradycardia (Purks, 1939). Because of this high incidence, we have used a shorter period of massage, believing this to be perhaps more akin to the clinical problem and knowing that prolonged massage may be hazardous (Goldenberger, 1963). It is impossible to get a truly standardised stimulus. However, carotid sinus massage was performed by one person only and, using this method, an abnormal response in the control group of patients in hospital was rare (2%). The 23 patients gathered from a general medical outpatient clinic complained of syncope, transient amnesia, light headedness, or vertigo. Several patients had been severely symptomatic for many years and five had been misdiagnosed as having epilepsy. Six patients volunteered that they had suffered from transient attacks of amnesia: case 7 could not remember playing a golf shot, and case 3, a garage mechanic, was frequently unable to recall what he had done after servicing cars in the garage pit. The other patients presented with syncope and less specific complaints, such as dizziness, light headedness, or vertigo. In cases 3 and 7, rotation or extension of the neck invariably produced symptomatic bradycardia.

In case 2, symptomatic bradycardia could be produced repeatedly when swallowing a glass of cold water. In other patients, such a clear association was not seen. However, carotid sinus massage reproduced symptomatic bradycardia in all patients and a high degree of vagal tone or responsiveness may have been responsible for their spontaneous symptoms.

Monitoring was performed in three ambulant patients, but episodic profound sinus bradycardia was observed in all cases. In the two patients (cases 2 and 8) who showed both carotid hypersensitivity and impaired sinus node automaticity it was possible to show that these were entirely separate phenomena by the use of atropine, though in the clinical situation these abnormalities may well have had an additive effect in the production of symptomatic bradycardia. It can be argued that by only estimating sinus node recovery time we are not excluding the presence of sinus node disease in the other eight patients studied (Gupta *et al.*, 1974) and that estimation of sinuatrial conduction time, as described by Strauss *et al.* (1973) or Narula *et al.* (1978), would have led to the identification of lesser degrees of sinus node disease. We do not believe that this is so or even relevant in patients with such profound symptomatic bradycardia related to excessive vagal responsiveness.

The estimation of sinuatrial recovery and conduction by electrophysiological methods has limited value, and we agree with Evans *et al.* (1978) that from the practical point of view the diagnosis of sick sinus syndrome is best made from the resting electrocardiogram together with ambulatory monitoring.

Before the widespread use of cardiac pacemakers for the treatment of bradycardia, the carotid sinus syndrome was treated by drugs such as atropine, amphetamines, ephedrine, or by irradiation or denervation of the carotid sinus (Thomas, 1969). Clearly, the most reliable method of treatment in such patients should be cardiac pacing. Until recently there have been isolated reports concerning the role of pacing in this condition.

More recent studies have reported the effect of pacing on carotid hypersensitivity often in association with episodes of complete atrioventricular dissociation (Voss and Magnin, 1970; Bahl *et al.*, 1971; Peretz *et al.*, 1973; Walter *et al.*, 1978).

In conclusion, our findings show that hypersensitivity of the carotid sinus reflex is present in a group of patients presenting with transient cerebral disturbances. There may, in addition, be intraventricular conduction disturbance or sinus node disease. However, some patients with severe symptoms may have a grossly abnormal response to carotid sinus massage in the presence of normal electrophysiology. Increased vagal tone or responsiveness as shown by our group of patients seems to be a relatively common mechanism in the production of symptoms in patients presenting to a general medical clinic. Further study is needed to determine the true prevalence of syncope in association with carotid sinus hypersensitivity. The technique of carotid sinus massage, as described, is simple and safe; we consider it worth while to include this procedure in the routine examination of patients who have a history of syncope.

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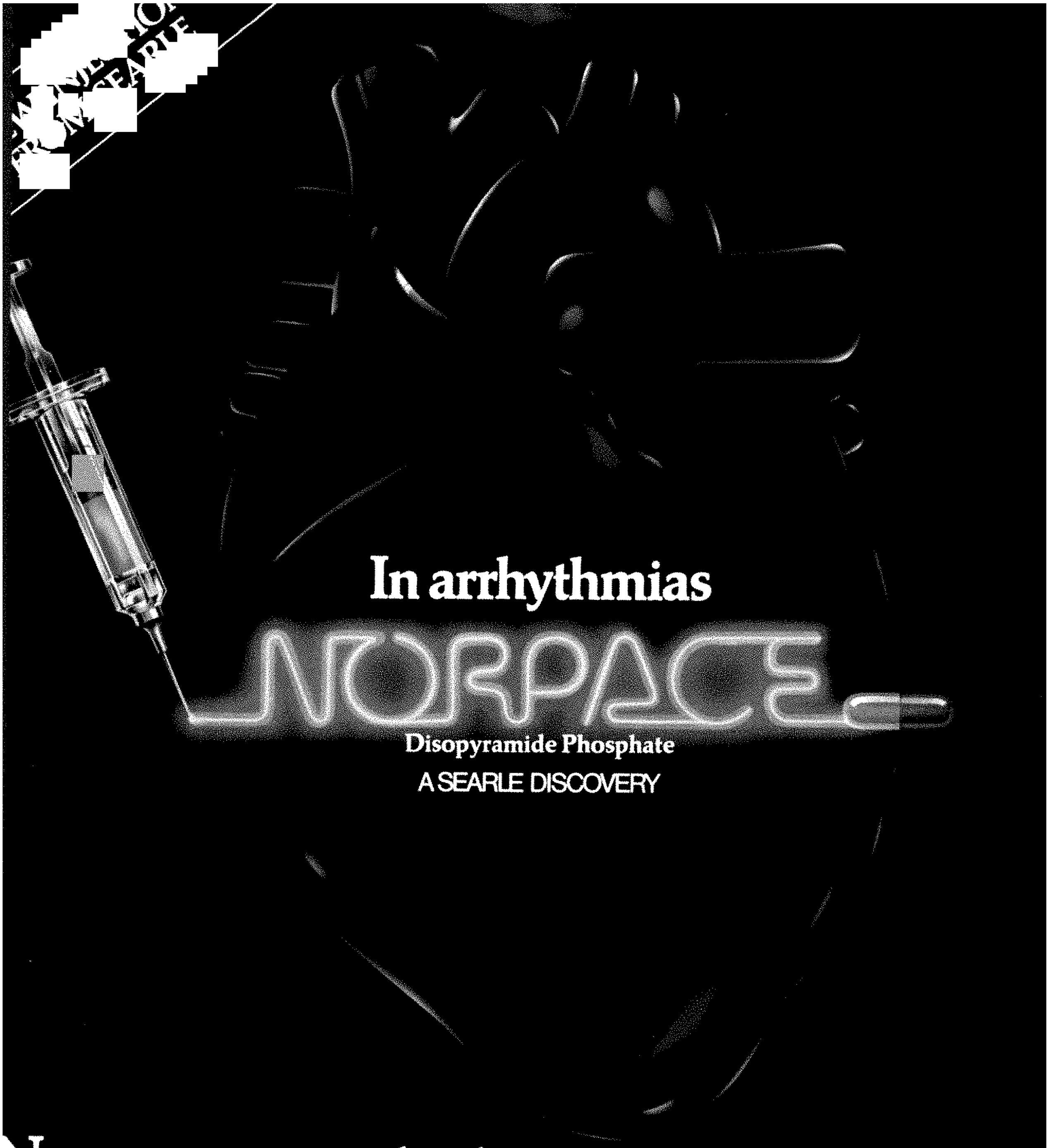

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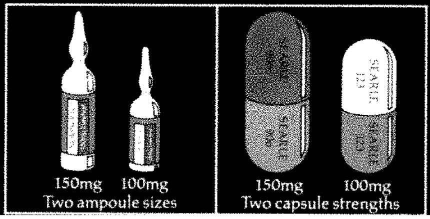

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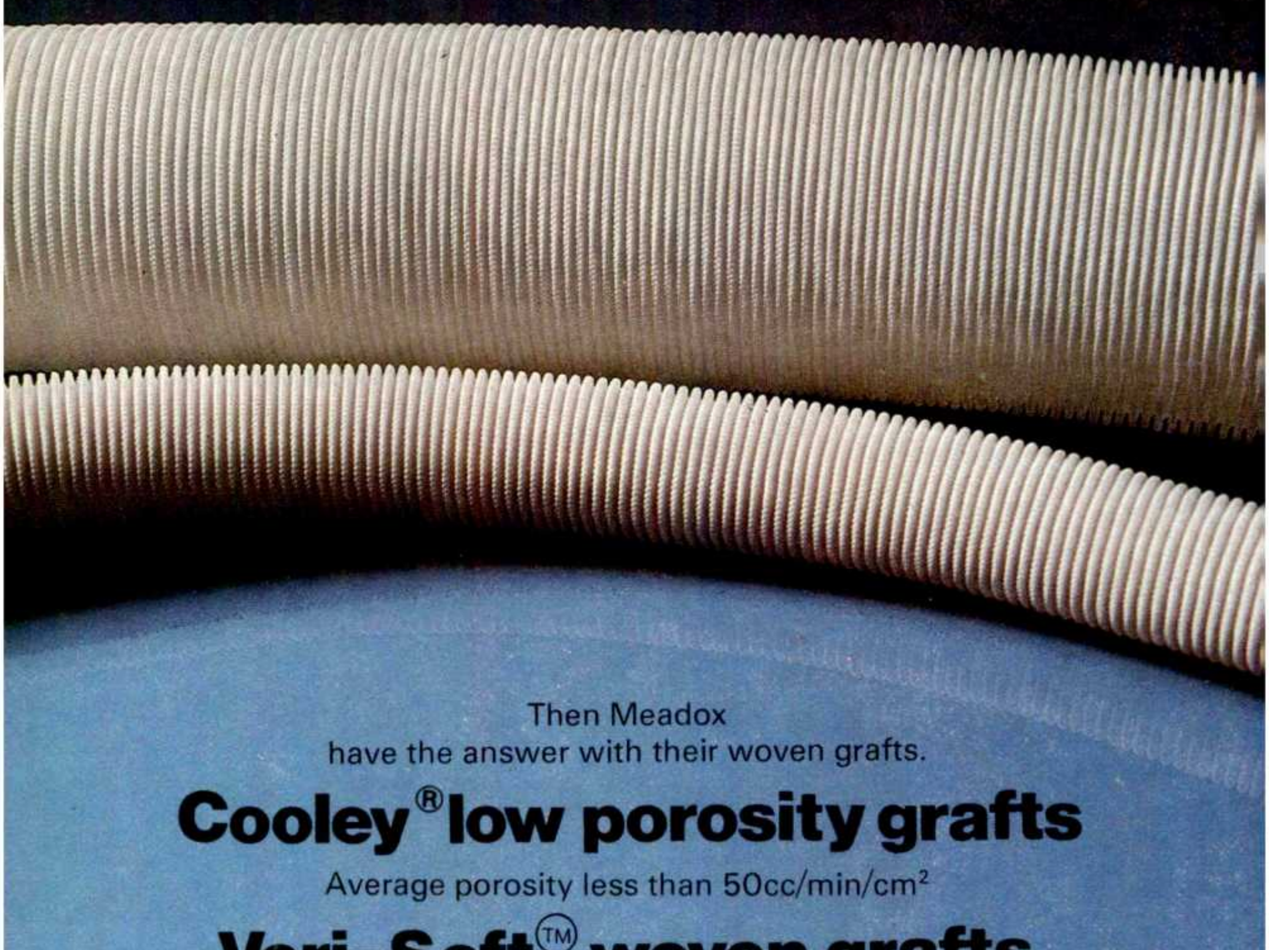

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British Heart Journal, 1979, **42**, 587–594

Haemodynamic effects of disopyramide in patients after open-heart surgery

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SUMMARY Disopyramide phosphate was administered intravenously in a dose of 1·2 mg/kg body weight over one minute to nine patients after open-heart surgery and coronary artery bypass grafting. The haemodynamic changes were studied during and for 30 minutes after drug administration. Heart rate was unchanged throughout the study. During infusion the only significant changes were an increase in systemic blood pressure and systolic impedance signifying a direct increase in peripheral arterial resistance. Systemic blood pressure remained significantly higher for 10 minutes and systolic impedance for 30 minutes. Immediately after infusion max. dPower/dT, a measure of ventricular contractility, was significantly depressed for 15 minutes. Both cardiac output and aortic flow were significantly depressed for 30 minutes. DPTI/TTI, an estimate of subendocardial supply/demand ratio, showed an insignificant increase throughout the study.

This study shows that intravenous disopyramide starts acting within 45 seconds of the start of infusion, directly increases peripheral arterial resistance, has a brief negative inotropic action, and does not reduce subendocardial blood flow.

Disopyramide (4 diisopropylamino-2-phenyl-2-(2-pyridyl) butyramide) has proved to be an effective new antiarrhythmic drug. Its efficacy in suppressing ventricular arrhythmias (Vismara *et al.*, 1974; Mizgala and Huvelle, 1976; Deano *et al.*, 1977) and, to a lesser extent, supraventricular arrhythmias (Lerch, 1976; Daly and Owens, 1977; Ward *et al.*, 1977) is well documented. Electrophysiological studies have shown a beneficial effect in Wolff-Parkinson-White syndrome (Spurrell *et al.*, 1975; Camm and Spurrell, 1977). It has been shown to be effective in the prophylaxis and treatment of arrhythmias occurring after myocardial infarction (Hillis *et al.*, 1976; Jennings *et al.*, 1976).

The haemodynamic effects of disopyramide phosphate (Norpace:Searle) given intravenously to nine patients after open-heart surgery and coronary artery bypass grafting are reported. The particular aims of the study were to measure the time of onset of action of disopyramide and the early haemodynamic changes after intravenous injection.

Subjects and methods

Nine patients with ischaemic heart disease undergoing coronary artery bypass grafting were recruited to the study. Prior informed consent was obtained.

Exclusion criteria included the following:

(1) Patients who had received digitalis glycosides within two weeks before the study.
(2) Patients who had received inotropic agents in the 30 minutes before the study.
(3) Patients receiving any other antiarrhythmic agent.
(4) Patients suffering from urinary retention (Large and Todd, 1977) or glaucoma (Trope and Hind, 1978).
(5) Patients with renal failure (Whiting and Elliott, 1977; Whiting and Miller, 1977).
(6) Patients receiving any anticholinergic drug.
(7) Patients with atrioventricular or severe intraventricular conduction defects (Niarchos, 1976; Croxson and Atkin, 1977).
(8) Patients with congestive cardiac failure.
(9) Patients who had a known sensitivity to disopyramide phosphate.

Before closure of the chest after the placement of the bypass grafts a rigid non-cannulating extractable electromagnetic blood flow probe (Carolina Medical Electronics 900 series) with suitable internal circumference was applied to the ascending aorta as previously described (Williams *et al.*, 1972;

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Farnsworth *et al.*, 1977). Details of the use of such a flow probe to assess myocardial performance in man are published elsewhere (Lewis *et al.*, 1978). The connections of the flow probe, and the monitoring equipment used in the study are detailed by Malcolm *et al.* (1977). It is pertinent to describe these briefly here. The flow probe was connected to a single channel patient isolated flow meter (Carolina Medical Electronics, 'Cliniflow' Model 601 D). Arterial pressure was monitored by a micromanometer (Millar Instruments, 'Mikro-Tip' Model 3EA/a) connected on to a three-way tap on a 16 or 18 gauge cannula placed either in the femoral or radial artery. Left atrial pressure was monitored via a fluid filled line which is routinely inserted through the posterior aspect of the left atrium at the end of operations involving cardiopulmonary bypass. The electrocardiogram was taken from an auxiliary socket on the electrocardiographic monitor normally used at the bedside. Pressure and flow signals and the electrocardiogram were displayed on a multichannel oscilloscope (Cardiac Recorders, eight channel, with Type 99 control unit) and recorded on magnetic tape with a seven-channel recorder (Philips 'Analog-7'). The oscilloscope tape recorder and the flow meter are mounted on a mobile trolley which has been described elsewhere (Bourne and Williams, 1975). Left atrial mean pressure was recorded verbally on the audio channel of the tape recorder at each point in the study so that it was subsequently available when data processing was done. Data stored on magnetic tape was processed 'off-line' using an analogue-to-digital converter interfaced with a Varian 620 L/100 digital computer. The output from the computer is provided in the form of teletype printing (for numerical data), hard copy prints of cathode ray tube displays (of waveforms, pressure volume plots, and associated numerical data), and paper tape (for numerical data, later to be used for statistical processing). Up to 18 seconds of data for each reading were transferred from tape to computer for analysis.

The following values for every heart beat during the 18 second sampling period were analysed:

Heart rate (beats per minute); duration of systole (seconds); stroke volume (ml); maximum pressure (mmHg); minimum pressure (mmHg); mean pressure (mmHg); maximum flow (litres/min); maximum rate of change of flow with respect to time, designated 'max. dF/dt'; percentage of stroke volume ejected during systole up to the time of maximum aortic flow, designated '% flow to max. flow'; percentage of stroke volume ejected during the first third of systole, designated '% flow to 33·3% syst.'; mean systolic impedance (Newtons/metre^5 per s) calculated as mean pressure during systole/mean flow during systole; impedance at maximum flow (Newtons/metre^5 per s) calculated as pressure at time of maximum flow/flow at time of maximum flow; stroke work (joules/beat) calculated as the time integral during systole of the product of developed pressure and flow; maximum left ventricular ejection power (Watts) calculated as the maximum value of the instantaneous product of pressure and flow; mean left ventricular ejection power; maximum rate of change of ejection power with respect to time, designated 'max dPower/dT' (Watts/s); cardiac output (litres/min); diastolic reverse flow (percentage of stroke volume); percentage of stroke volume ejected up to the time of maximum rate of change of flow, designated '% flow to max. acceleration'; ratio of diastolic pressure time index/systolic tension time index, designated 'DPTI/TTI'.

Patients were studied when they had been in the intensive care unit for eight to 12 hours after open-heart surgery and all values of cardiovascular function were stable and satisfactory. No other medication was given for at least half an hour before and during the study. 10 ml venous blood were withdrawn into a heparinised tube for pretreatment

Table *Clinical details of patients studied*

Case no.	*Age (y)*	*Sex*	*Wt (kg)*	*Cardiac catheterisation data*				
				Cardiac index (ml/min per m²)	*LVEDP (mmHg)*	*LVEDV (ml/m²)*	*EF*	*Coronary artery disease*
1	56	M	87	3·5	7	89	0·76	Triple vessel
2	56	M	75	2·3	4	78	0·51	RCA
3	62	M	83	2·3	5	64	0·64	Triple vessel
4	58	M	94	2·7	8	60	0·55	LAD circumflex
5	25	M	66	3·4	9	85	0·85	Triple vessel
6	39	M	75	2·4	8	84	0·75	LAD
7	53	M	75	2·5	5	86	0·76	LAD RCA
8	60	M	82	3·0	4	61	0·57	Triple vessel
9	47	M	83	3·3	5	58	0·76	LAD circumflex

LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; EF, ejection fraction; LAD, left anterior descending artery; RCA, right coronary artery.

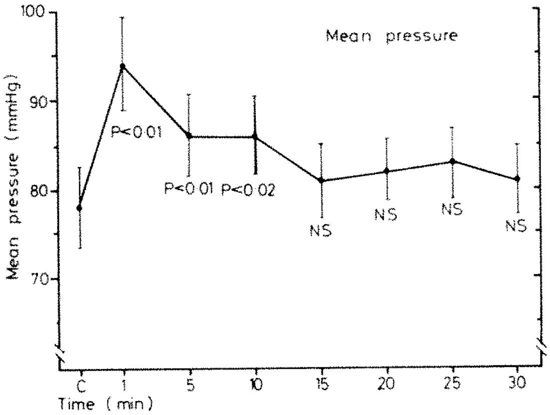

Fig. 1 *Changes in mean pressure (±SEM) after disopyramide. C, control; NS, not significant; SEM, standard error of mean.*

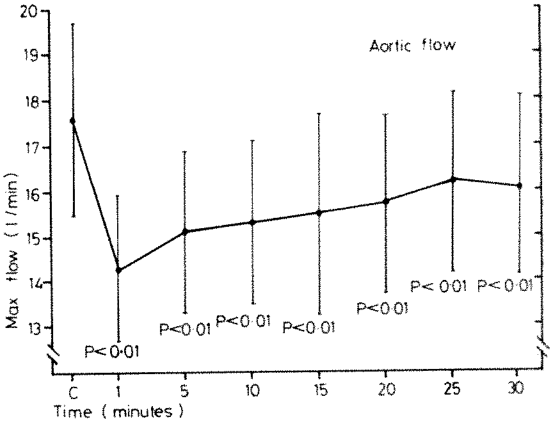

Fig. 2 *Changes in maximum aortic flow (±SEM) after disopyramide. C, control, SEM, standard error of mean.*

drug assay. Three to five control readings were taken, each at five-minute intervals. If the control readings were comparable, disopyramide phosphate (Norpace:Searle) was given intravenously in a dose of 1·2 mg/kg body weight over a period of one minute. Readings were started at the beginning of the infusion and continued throughout the infusion to enable the time of onset of action of the drug to be measured. Thereafter readings were taken at one-minute intervals for 10 minutes and then at five-minute intervals for the next 20 minutes. 10 ml venous blood were withdrawn for drug assay at five, 10, 15, 20, and 30 minutes into heparinised tubes. These samples were centrifuged within a few minutes of collection and the plasma stored at −20°C for subsequent drug assay.

Student's t test for paired samples was used to determine the significance of changes from pre-infusion values, each patient acting as his own control. Values are expressed as mean ± standard error of the mean, and a P value $< 0{\cdot}05$ is considered significant.

The clinical details of the patients studied are given in the Table.

Results

There was no significant change in heart rate or duration of systole. The mean heart rate at one minute had increased by 4·9 per cent but this was not statistically significant. Thereafter there was no change in heart rate. At 30 minutes the mean heart rate had decreased by an insignificant 1·8 per cent.

The changes in mean blood pressure are shown in Fig. 1. There was an increase in systolic, diastolic, and mean readings which was greatest at one minute after the onset of infusion. At five minutes the increase was much less and was not significant for the systolic pressure. The increase in diastolic and mean pressure remained highly significant for up to 10 minutes. The percentage increase in the systolic, mean, and diastolic pressures at one minute were 16, 22, and 28, respectively. After 10 minutes the increase in mean pressure was not statistically significant. The immediate rise in pressures was followed by an initial rapid and then gradual fall towards control values though the latter were not reached even at 30 minutes. The mean pressure at 30 minutes was 5·2 per cent greater than control values.

Changes in maximum flow are recorded in Fig. 2.

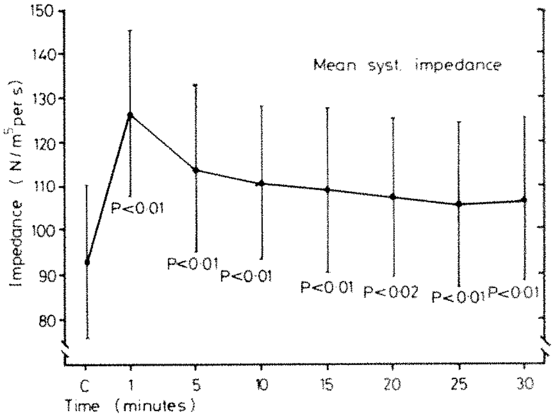

Fig. 3 *Changes in mean systolic impedance (±SEM) after disopyramide. C, control; SEM, standard error of mean.*

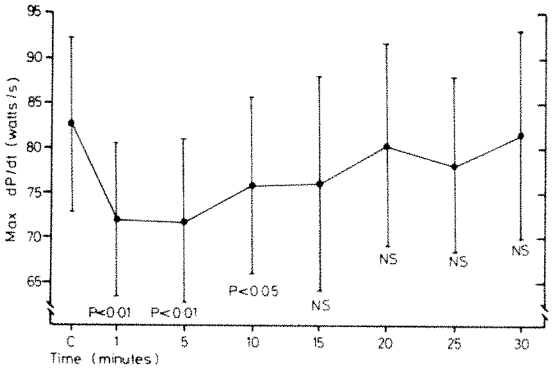

Fig. 4 *Changes in max. dPower/dT (±SEM) after disopyramide. C, control; NS, not significant; SEM, standard error of mean.*

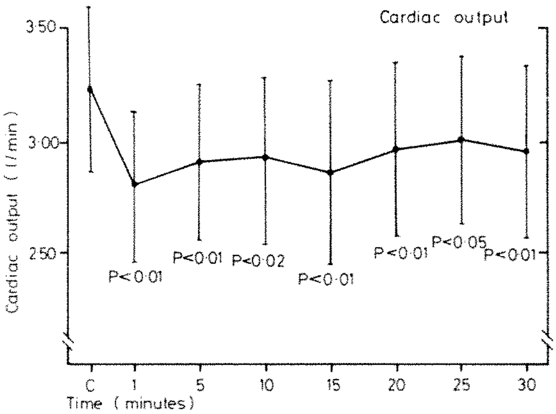

Fig. 5 *Changes in cardiac output (±SEM) after disopyramide. C, control; SEM, standard error of mean.*

Maximum flow remained significantly depressed throughout the 30 minutes of the study. The maximum depression was at one minute, a mean decrease of 18·8 per cent as compared with control values, but even at 30 minutes maximum flow was still 8·5 per cent less than control values. Per cent flow to max. flow and per cent flow to max. acceleration did not show any significant change. Though diastolic reverse flow lessened, this did not reach statistical significance. Max. dF/dT remained significantly depressed compared with control values throughout the study.

Mean systolic impedance, shown in Fig. 3, increased strikingly and this increase remained statistically significant throughout the study, the maximum increase occurring at one minute after the onset of drug infusion and the mean increase being of the magnitude of 35 per cent compared with control values. Again a gradual drift towards control values occurred, but at 30 minutes was still increased by 14·5 per cent. Impedance at maximum flow remained significantly raised throughout the study after the drug infusion.

Max. dPower/dT, a measure of ventricular contractility (Stein and Sabbah, 1976), was initially depressed after drug infusion but by 30 minutes had returned almost completely to control values (Fig. 4). The difference was not statistically significant after 15 minutes. The percentage change from control values was 12, 13·5, 8·4, 8·4 at one, five, 10, and 15 minutes, respectively.

Cardiac output was reduced after drug infusion (Fig. 5). This reduction was greatest (13·3%) at one minute and remained significantly depressed for 30 minutes. By 30 minutes the mean depression was 8·6 per cent. As expected, changes in stroke volume merely reflected the changes in cardiac output since there was no significant change in heart rate.

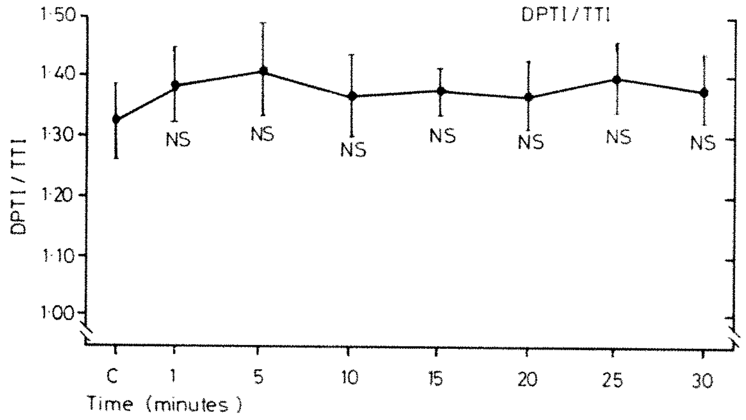

Fig. 6 *Changes in DPTI/TTI (±SEM) after disopyramide. C, control; NS, not significant; SEM, standard error of mean.*

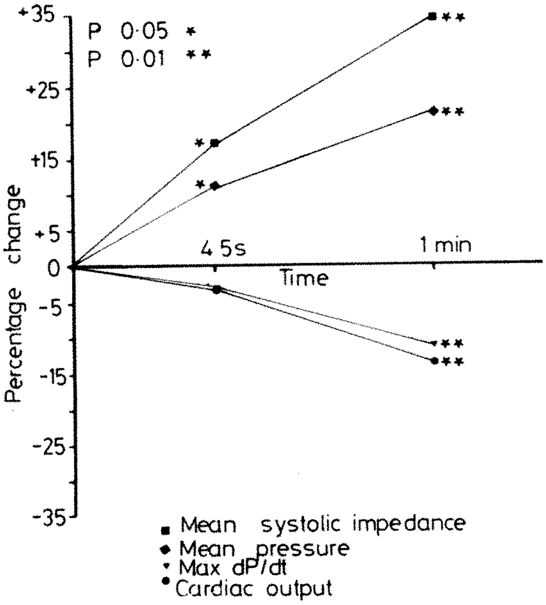

Fig. 7 *Changes during and immediately after disopyramide infusion. See text for details.*

Although maximum LV ejection power showed an initial depression after drug infusion, this was not statistically significant. The changes in mean LV ejection power were inconstant and were not statistically significant. There was no statistically significant change in stroke work.

The ratio DPTI/TTI, which is an estimate of subendocardial supply/demand relation (Buckberg *et al.,* 1972; Hoffman and Buckberg, 1978), is shown in Fig. 6. At one minute after the start of drug infusion there was a 4·5 per cent increase but this was not statistically significant. Thereafter the increase remained steady at around 4 per cent.

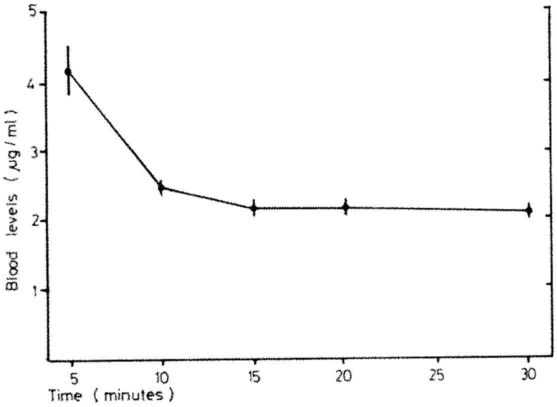

Fig. 8 *Blood levels (±SEM) of disopyramide. SEM, standard error of mean.*

Changes occurring during drug administration were monitored in seven patients. There was no significant change in any of the values during the first 30 seconds. The changes that occurred between 30 and 50 seconds after the start of drug infusion are shown in Fig. 7. The increase in mean pressure and mean systolic impedance was significant ($P < 0{\cdot}05$), the percentage change being 10·3 and 17, respectively. There was no significant change in cardiac output and max. dPower/dT at this time.

There was no change in left atrial or right atrial pressure at any stage after drug administration.

The blood levels of disopyramide, determined by the method of Hutsell and Stachelski (1975), are given in Fig. 8.

Discussion

Before discussing the haemodynamic effects of disopyramide certain facts need to be clarified. We believe, like Slogoff *et al.* (1977), that continued treatment with beta-blocking drugs before open-heart surgery is beneficial and hence continue beta-blockade until the time of surgery. Some negative inotropic effect from these drugs will inevitably be present for some time during the postoperative period. Jenkins *et al.* (1973) have claimed that it is possible that the period of cardiopulmonary bypass is a further contributory factor to myocardial depression immediately after surgery regardless of previous cardiac pathology, and in the majority of patients studied by them the ventricular function curves were relatively flat. Hence, in our patients some depression of myocardial function may well have been present before disopyramide was administered. However, our study is particularly relevant since this is just the situation in which disopyramide is often used, that is after open-heart surgery, after myocardial infarction complicated by arrhythmias, etc.—situations where myocardial depression is often an important factor.

The other point to be noted is that the dose of disopyramide used in this study was fairly modest. However, the plasma levels of the drug were within the accepted therapeutically effective range which is between 2 and 4 μg/ml (Karim, 1975; Rangno *et al.,* 1976). The fact that the drug was given over one minute and not longer could well have contributed to the extent of the changes seen at the one-minute period.

In animal experiments disopyramide has been shown to have a weak negative inotropic effect (Mokler and Van Arman, 1962; Mathur, 1972;

Nayler, 1976). Baines *et al.* (1976) using beagle dogs found that intravenous disopyramide reduced cardiac output by 9 to 22 per cent, depressed cardiac contractility, reduced coronary flow, and produced only small inconstant changes in heart rate.

Changes in systemic blood pressure after disopyramide administration have varied in different series. The variability is probably attributable to differences in left ventricular function of the patients studied. A fall in blood pressure was found by Jensen *et al.* (1975) in patients who had imminent or manifest heart failure, and by Sutton (1976) in patients with abnormal left ventricular function. Hulting and Rosenhamer (1975) found no significant change in mean arterial pressure measured five and 10 minutes after drug administration, but from the twentieth minute to the end of the observation period (180 minutes) mean arterial pressure was significantly increased above control values. Befeler (1975) and Marrot *et al.* (1976) have reported a rise in blood pressure after disopyramide administration. We found an immediate rise in systolic, diastolic, and mean pressure which was maximal at one minute, and these pressures, though returning towards control values, remained raised throughout the study. At five minutes the rise in blood pressure was only marginally more than that in Marrot *et al.'s* study (1976)—7, 14, and 11·7 per cent compared with 7, 10, and 7 per cent in systolic, diastolic, and mean blood pressures, respectively. Initially it was thought that the increase in blood pressure was a reflex response to the lowering of cardiac output (Befeler, 1975). However, during infusion of the drug there was a significant rise in mean pressure and mean systolic impedance (Fig. 7). There was no decrease in rate of change of power and the change in cardiac output was not significant. Hence the significant early change in systemic pressure and systolic impedance but not in cardiac output and max. dPower/dT suggested that the increase in blood pressure was not a reflex response to lowering of cardiac output but occurred independently and presumably was a result of increased peripheral vascular resistance. Vismara *et al.* (1975) have shown that disopyramide directly increased vascular resistance. As expected, increase in afterload raised the peak ventricular and aortic pressure and decreased the peak flow (Milnor, 1975).

Most haemodynamic studies agree that disopyramide is a negative inotropic agent (Jensen *et al.*, 1975; Hulting and Rosenhamer, 1975; Marrot *et al.*, 1976). This was confirmed in our study where max. dPower/dT was reduced by 12 per cent and cardiac output by 13·3 per cent at one minute after the onset of infusion of the drug. Though cardiac output alone may be depressed by increases in afterload, max. dPower/dT is not, being independant of afterload (Stein and Sabbah, 1976), confirming that disopyramide has a negative inotropic action. Significant depression of max. dPower/dT was shortlived and the reduction in cardiac output was less than 10 per cent after 15 minutes. Hence the negative inotropic action of disopyramide is transient, and progressively diminishes in intensity.

In most studies there has been no significant change in heart rate in patients in sinus rhythm (Jensen *et al.*, 1975; Hillis *et al.*, 1976; Marrot *et al.*, 1976). This was found in our study as well. Since disopyramide is known to have weak anticholinergic properties (Baines *et al.*, 1976; McHaffie *et al.*, 1977) some increase in heart rate might be expected. However, the early increase in systolic impedance and systemic blood pressure would reflexly slow the heart. It is possible that this, perhaps coupled with the membrane stabilising effect of the drug (Reid and Williams, 1977), would oppose the vagolytic effect and result in no change in heart rate.

Finally, our results of DPTI/TTI show that there is no deterioration in subendocardial blood flow after disopyramide administration. At all times after disopyramide there was an increase in the ratio, varying from 3 to 6 per cent, though this was not statistically significant. This is of considerable benefit when disopyramide is given to patients with anaemia, aortic valve disease, coronary atherosclerosis, acute myocardial infarction, or after cardiac surgery. All these conditions are known to be associated with impairment of blood supply to the subendocardial region (Hoffman and Buckberg, 1975). We wish to point out that in our study the ratio DPTI/TTI has been derived by assuming that recorded peripheral arterial pressure waveform during systole is identical in pressure values at every instant with the pressure waveform in the aorta and left ventricle, and that the mean left atrial pressure is a valid approximation to left ventricular end-diastolic pressure.

We have thus shown that disopyramide has a brief negative inotropic action, that it increases peripheral arterial resistance for at least 30 minutes, and that it does not reduce subendocardial blood flow. The onset of action of the drug is within 45 seconds of the start of intravenous infusion.

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Clinical and electrophysiological characteristics of a transvenous atrial lead

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SUMMARY Despite some reports on the use of the atrial transvenous endocardial lead, Medtronic 6991, there is still very little information on the electrophysiological properties of the lead. A lead extension wire was connected to the atrial lead, passed subcutaneously, and brought through the abdominal skin. P wave amplitude, threshold of stimulation, and electrode resistance were repeatedly determined through the atrial lead during four weeks after the electrode insertion in 17 patients. Mean P wave amplitude at insertion was 3·7 ± 1·0 (mean ± SD) mV. It decreased significantly to a lowest mean level of 2·3 ± 0·9 mV after one week. From that time there were only small variations. In the supine position and with normal breathing there was a spontaneous variation in the P wave amplitude of ± 15 per cent. P wave amplitude was only to a minor extent influenced by body position and maximum breathing movements. The threshold of stimulation was 1·7 ± 0·7 V (impulse duration 0·5 ms) at the time of electrode insertion. It increased to 2·7 ± 1·0 V after four weeks. The electrode resistance varied about 600 ohms.

A total of 28 patients received an atrial transvenous endocardial lead. Three electrode dislocations occurred, all during the first 24 hours; apart from these three, the electrodes were connected easily to the intended pacemakers and have functioned well during the observation period of between two and 24 months. In conclusion, the transvenous endocardial atrial lead Medtronic 6991 has shown attractive qualities. The electrophysiological data recorded are suitable for the pacemakers in use. So far this atrial lead seems promising and deserves further evaluation.

Despite the increasing number of patients with pacemakers, there has not been a corresponding increase in the use of atrial synchronous and atrial inhibited pacing. In Sweden not more than 1 per cent of initially implanted pacemakers are atrial synchronous (Karlöf and Lagergren, 1973; Edhag, 1977). Many patients would, however, improve haemodynamically with an atrial inhibited or atrial synchronous pacemaker (Lagergren *et al.*, 1966; DeSanctis, 1971; Furman, 1973). The reason for the limited use of atrial pacing is probably the lack of an electrode which combines a simple technique of introduction with long-term reliability. Recently promising results have been reported by the use of a transvenous J-shaped atrial tined lead (Smyth *et al.*, 1976; Kleinert *et al.*, 1977). These reports deal with the technique of introduction and electrophysiological characteristics of the lead at the time of electrode insertion.

The present investigation was undertaken to study the electrophysiological characteristics of the atrial electrode by means of repeated measurements throughout a period of four weeks after the introduction of the electrode. The report also contains information about our present clinical experience with the electrode.

Subjects and methods

PATIENTS

The subjects consisted of 28 patients; pertinent data from these are presented in Table 1.

THE LEAD

The lead (Medtronic model 6991) has a unipolar electrode and is designed for transvenous introduction. It is made of a silicone rubber-insulated nickel alloy lead which ends in a $10\ mm^2$ platinum electrode tip. The distal part of the electrode is preformed like a J the radius of which is 1·3 cm. The short leg of this J is furnished with nine tines of silicon rubber. The J-shape and the tines facilitate fixation of the electrode tip within the right atrial

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appendage. The first five leads were used unmodified. Subsequently the tines were trimmed. In the beginning this trimming gave the tines the shape of a 'Christmas-tree'. The trimming of the lead has become increasingly more pronounced. Thus, in the last five patients only 5 mm have been left of the three tines closest to the electrode tip while the others have been cut away entirely (Fig. 1).

The electrode has usually been introduced via the external jugular vein (19 patients). The internal jugular vein (five patients) or the cephalic vein (four patients) have been used when the external jugular vein was too small. During the introduction the distal portion of the lead has been straightened by means of a stylet. This is withdrawn as soon as the lead has reached the right atrium. When the distal part of the electrode has recovered the J-shape, the lead is rotated in order to position the tip in an anterior and medial direction. Thereafter the lead is slightly withdrawn. During this procedure the electrode tip usually recoils by itself into the right atrial appendage.

The electrode position has been accepted when the tip of the electrode points medially and anteriorly, swings sideways with each atrial contraction, and only makes minor movements within the right atrial appendage while the patient takes a deep breath or is coughing. The J-shape should be maintained during maximal breathing movements. Finally it should be possible to record a stable atrial electrogram through the lead. A typical electrode position is shown in Fig. 2. After obtaining a stable electrode position the lead has been fixed at the site of entry into the vein by means of an anchoring sleeve.

ELECTROPHYSIOLOGICAL MEASUREMENTS

At the time of introduction the atrial lead was connected to a lead extension wire in 17 of the patients. This was passed subcutaneously and externalised through the abdominal skin. Patients in whom a pacemaker was implanted previously retained this wire during the investigation period. In these cases the extension lead was removed at the time of pacemaker replacement. In other patients the final pacemaker was implanted directly. In these, a specially constructed extension lead made it possible to extract it by means of direct traction.

P wave amplitude, threshold of stimulation, and total electrode resistance were measured repeatedly during the first week and subsequently once a week during one month after lead insertion. The measurements were performed with the patients in the supine position and with normal breathing. A basic P wave amplitude was determined as the mean value of five consecutive P waves. Furthermore, changes in P wave amplitude during maximum inspiratory and expiratory apnoea and in different body positions (standing, sitting, lying on left and right side) were determined as the maximal percentage change from the basic P wave amplitude. The P waves were measured by means of a Mingograph 82 (Siemens-Elema, Sweden), with a frequency response 0 to 1250 Hz. All P wave recordings were bipolar with the reference point (needle electrode) below the clavicle at the site of pacemaker implantation. The stimulation threshold of the atrium was determined by means of the Medtronic 5300 Pacemaker System Analyzer. The threshold was determined at a stimulation impulse duration of 0·2; 0·4; 0·5;

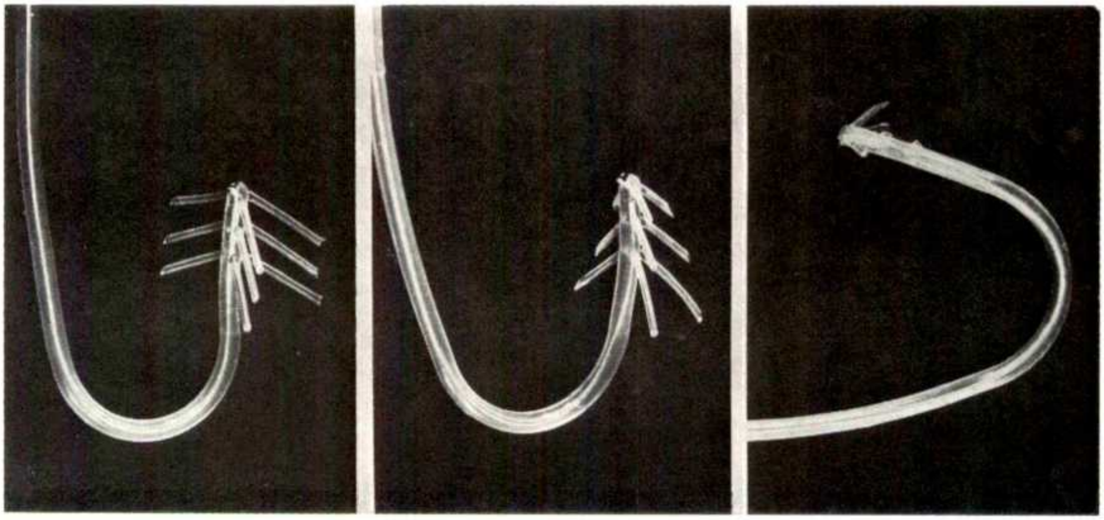

Fig. 1 *Differently trimmed electrode tips. The picture on the right shows the present degree of trimming.*

1·0; and 1·5 ms. The threshold was defined as the minimal impulse amplitude constantly stimulating the atria. The threshold was determined in volts and resulting current. The electrode lead resistance was determined at a stimulation impulse duration of 0·5 ms and at an impulse amplitude of 5·0 V.

Statistical analysis was performed using Student's t test for paired differences, and a P value of $<0{\cdot}05$ was accepted as statistically significant.

Results

P WAVE AMPLITUDE

The variation of the P wave amplitude versus time is presented in Fig. 3. The mean P wave amplitude ±SD for the group at the time of insertion was 3·7 ± 1·0 mV. Thereafter it decreased significantly ($P < 0{\cdot}01$) to a lowest mean level 2·3 ± 0·9 mV after one week. From that time there were only small

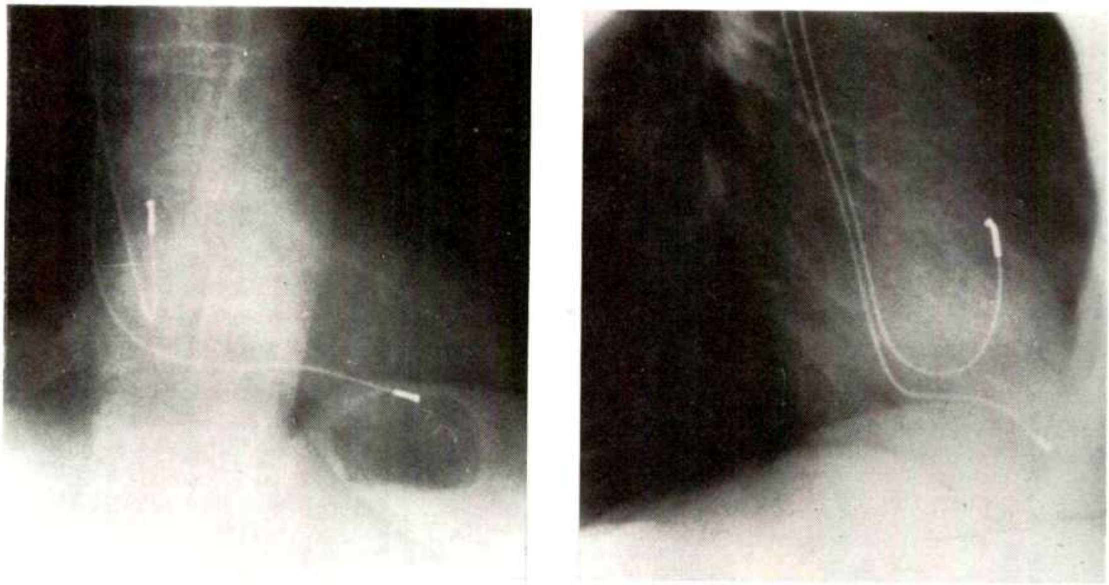

Fig. 2 *A typical position of the J electrode in the right atrial appendage. The right and left panels show respectively lateral and frontal planes.*

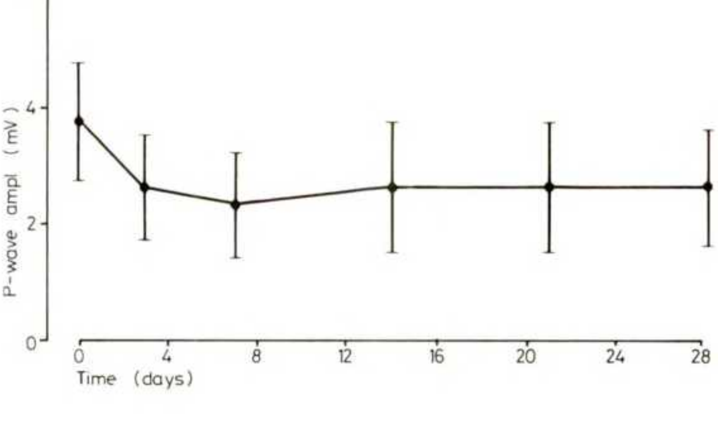

Fig. 3 *P wave amplitude in mV from the time of lead introduction and during four weeks. Mean value ±SD.*

changes during the remaining part of the observation period. These changes were not statistically significant. In Fig. 4 individual P wave amplitudes are presented at the time of electrode insertion and after one and four weeks. All patients except one have an initial P wave amplitude of at least 2·0 mV. In every case the P wave decreased from the moment of insertion to a stable level after one week. The mean reduction is about 40 per cent.

Fig. 5 presents individual spontaneous P wave variations during normal breathing with the patient in the supine position. The variation presented is the deviation (±) from the basic P wave level mentioned above (that is the mean of five consecutive P waves). In general the spontaneous variation is about ±15 per cent from this basic level. Though the variability decreases a little with time this difference is not statistically significant. When the P wave amplitude was recorded during maximal inspiration and expiration, with the patient in the supine position, lying on the right or left side, sitting, or standing, there were some variations in the P wave amplitude. These activities, however, did not induce deviations exceeding those reported during normal breathing in the supine position.

In Fig. 4 to 5 the numbers of patients observed are not in accordance with the total numbers of patients listed in Table 1. The electrophysiological investigations during four weeks were performed in 17 patients receiving a J electrode. In some of them a fracture of the extension wire prevented further measurements.

ATRIAL STIMULATION THRESHOLD

The stimulation threshold of the right atrium could only be determined in seven patients in whom continuous ventricular pacing did not make it impossible to detect stimulated P waves and/or stimulation of the right atrium did not inhibit the pacemaker in use.

The threshold of stimulation at an impulse duration of 0·5 ms was initially 1·7 ±0·7 V (mean ± SD), increased to 2·5 ±0·9 V after one week, and 2·7 ±1·0 after four weeks (Fig. 6). This increase did not reach statistical significance. The strength duration curves at the time of lead insertion and after four weeks are presented in Fig. 7. The curve obtained after one week was practically similar to the one at four weeks. The total resistance of the electrode system was about 600 ohms throughout the time of observation (Table 2).

CLINICAL EXPERIENCE

The insertion of the electrode was usually an easy procedure. The mean time of positioning the electrode within the right atrial appendage was 10 to 15 minutes measured from the opening of the vein. In two of the patients it was difficult to obtain a suitable electrode position. The operative procedure was then prolonged to about one hour. So far it has been possible to position an atrial lead in all cases where this has been indicated. The atrial electrode

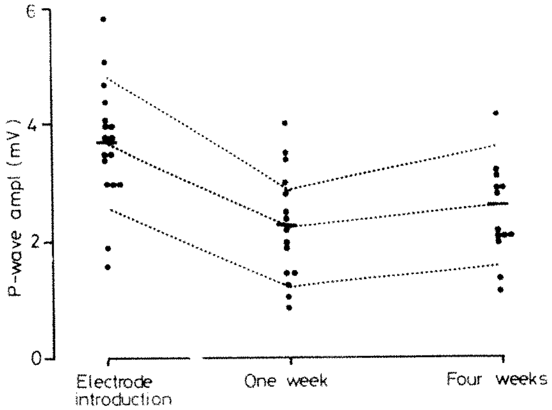

Fig. 4 *P wave amplitude in mV at the time of lead insertion and one and four weeks thereafter. Individual values are presented together with the mean ±SD for the total group of patient .*

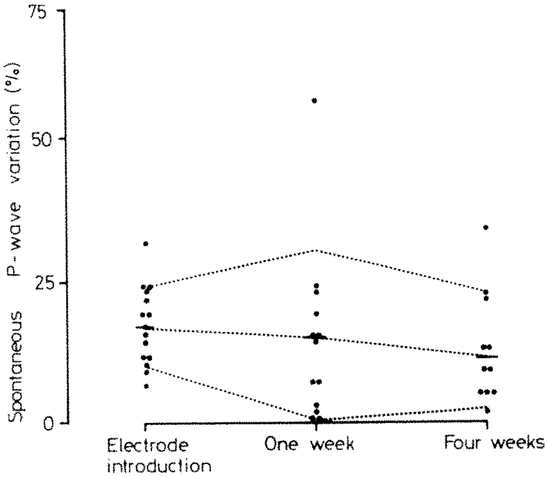

Fig. 5 *Spontaneous P wave variation at the time of lead insertion and one and four weeks thereafter. Individual values are presented, together with the mean ±SD for the total group of patients. The deviation (±) from the mean P wave amplitude is given in per cent along the vertical axis.*

has functioned well in all cases. One patient (case 1) received a VVI pacemaker when he later developed repeated attacks of atrial fibrillation. These were not related to the introduction of the atrial lead.

The electrode was dislodged in three cases (cases 4, 5, and 8). All dislodgements occurred within 24 hours after the positioning. In one patient a poor fixation of the electrode at the site of introduction into the internal jugular vein probably contributed (case 5). In case 4 there was a large difference between the position of the heart in the standing and supine position. In this patient the electrode dislodged when the patient got up for the first time after the operation. Probably the lead became too stretched within the atrium in the upright position. The explanation of the electrode dislodgement in case 8 was probably that a previously placed ventricular lead had developed a loop within the right atrium because the heart size had diminished. This loop 'whipped' the J lead with every heart beat resulting in dislodgement. Before repositioning of the atrial lead the ventricular lead was retracted in order to eliminate the loop. All the electrodes that were dislodged were easily repositioned and have thereafter functioned properly. The observation time at the end of December 1978 is presented in Table 1.

Apart from leads becoming dislodged there have been no complications related to the use of the atrial electrode. In one patient (case 12), atrial synchronous pacing was started as one of several attempts to relieve advanced left ventricular failure. This patient died about one month after lead insertion. At necropsy there were no signs of irritation or thrombus formation around the tip of the electrode. Only the tines closest to the tip of the electrode were positioned within the right atrial appendage, while the other tines were outside.

Discussion

Different methods have been used for the introduction of atrial electrodes. The electrode can be sutured to the atrial wall via a thoracotomy (Center *et al.*, 1963; Center and Nathan, 1966). Another approach is the mediastinal by means of mediastinoscopy as outlined by Carlens *et al.* (1965). Though this method has proved reliable with P wave sensing (Carlens *et al.*, 1977), it is not suitable for atrial pacing. A thoracotomy implies major surgery and though mediastinoscopy is not a particularly large operative procedure it requires general anaesthesia. Such factors have obviously limited the widespread use of these methods for atrial pacing and sensing. The transvenous route does overcome such restrictions. Early experiences with transvenous atrial electrodes were discouraging because of a high proportion of electrode dislodgement and increase in pacing threshold (Rodewald *et al.*, 1964; Center *et al.*, 1967; DeSanctis, 1971). One way of overcoming these problems is the use of

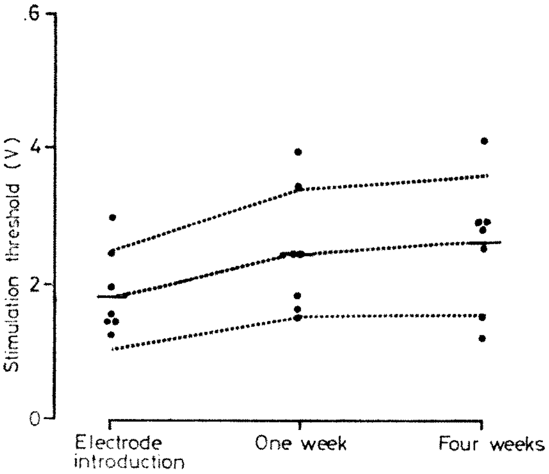

Fig. 6 *Right atrial stimulation threshold in volts (V) at an impulse duration of 0·5 ms at the time of lead insertion and one and four weeks therafter. Individual values are presented together with the mean ± SD for the total group of patients.*

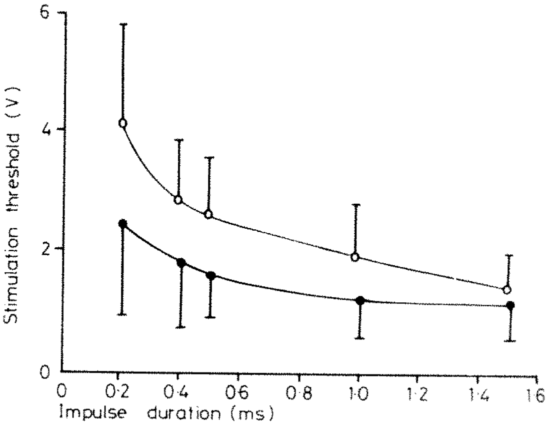

Fig. 7 *Strength duration curves in the right atrium. Stimulation threshold in volts (V) ± SD along the vertical axis and impulse duration in milliseconds along the horizontal.* ●*, at time of lead insertion;* ○*, four weeks after lead insertion.*

Table 1 *Selected data from patients (as per December 1978)*

Case no.	*Age (y)*	*Sex*	*Diagnosis*	*Arrhythmia*	*OBS time (mth)*	*Type of pacemaker**	*Remarks*
1	86	M	Coronary heart disease, myocardial infarct	AV II°–III°	24	VVI	Developed atrial fibrillation
2	62	M	AV conduction disturbance	AV III°	22	VDT/I	
3	65	M	Coronary heart disease, myocardial infarction	Excessive bradycardia upon carotid stimulation	22	VAT	
4	64	F	AV conduction disturbance	AV III°	20	VDT/I	Dislocation
5	67	M	AV conduction disturbance	AV III°	19	VDT/I	Dislocation
6	65	F	AV conduction disturbance	AV I°–II°	19	VDT/I	
7	59	F	AV conduction disturbance	AV III°	19	VDT/I	
8	82	F	Sick sinus syndrome	SA	17	AAI	Dislocation
9	59	M	Cardiomyopathy	AV III°	16	VDT/I	
10	63	F	Sick sinus syndrome	SA	16	AAI	
11	60	F	AV conduction disturbance	AV III°	14	VDT/I	
12	76	M	Coronary heart disease, myocardial infarction	AV III°	1	VDT/I	Dead
13	67	F	AV conduction disturbance	AV III°	10	VDT/I	
14	69	M	AV conduction disturbance	AV III°	10	VAT	
15	44	M	AV conduction disturbance	AV III°	10	VDT/I	
16	69	F	Perimyocarditis	AV III°	10	VDT/I	
17	55	F	AV conduction disturbance	AV I°–III°	9	VDT/I	
18	65	M	Hypertension, AV conduction disturbance	AV III°	9	VDT/I	
19	77	M	AV conduction disturbance	AV III°	8	VDT/I	
20	63	M	AV conduction disturbance	AV III°	8	VDT/I	
21	49	F	AV conduction disturbance VPC	AV II°–III°	7	VAT	
22	67	M	Sick sinus syndrome	SA	7	AAI	
23	79	F	Sick sinus syndrome	SA	6	AAI	
24	70	M	AV conduction disturbance	AV III°	6	DDT/I	Replaced by VAT
25	64	M	AV conduction disturbance	AV III°	5	VDT/I	
26	58	F	AV conduction disturbance	AV III°	4	VDT/I	
27	58	M	AV conduction disturbance	AV III°	3	VDT/I	
28	57	F	AV conduction disturbance	AV III°	2	VAT	

*According to Parsonnet *et al.* (1974).
AV I°–III°, atrioventricular block of the first-third degree; SA, sinus arrest; VPC, ventricular premature capture.

Table 2 *Electrode resistance (Ω) at various times after electrode insertion*

	At insertion	*1 week*	*4 weeks*
Mean	575	590	728
SD	221	210	267
no.	7	6	7

coronary sinus leads (Moss, 1975; Moss and Rivers, 1977). Another approach has been the design of preformed so-called J leads (Kastor *et al.*, 1969; Smyth *et al.*, 1969, 1971; Geddes *et al.*, 1978). The introduction of small hooks at the electrode tip is another method of increasing the stability of the electrode position within the right atrium originally suggested by Rosenkranz and Schaldach (1971) and further improved by Funke and Schaldach (1977).

The lead used in the present investigation was designed by Smyth *et al.* (1976). It presents a preformed J shape with three rows of tines close to the electrode tip. Both these qualities are intended to facilitate the anchoring of the lead within the right atrial appendage where the tines may entangle with the trabeculae. Promising clinical results with this lead have also been presented by Kleinert *et al.* (1977) and Citron *et al.* (1978).

The clinical experiences obtained in the present series of patients are in good agreement with the findings in previous reports. The lead is usually easy to position within the right atrial appendage and the subsequent function has been satisfactory during a mean observation period of 11 months (range two to 24). Of the three lead dislodgements, probably at least two (cases 4 and 5) were related to the early operative technique. A 10 per cent dislodgement rate in total may seem discouraging. It should, however, be remembered that repositioning was a simple procedure resulting in stable function and that there has been no displacement in the last 20 patients. In the previous reports on the lead the dislodgement rate varies between 0 and 6 per cent (Smyth *et al.*, 1976; Kleinert *et al.*, 1977; Citron *et al.*, 1978). In the patient who died (case 12) it was obvious that only the tines closest to the electrode tip were entangled in the trabeculae of the right atrial appendage while the other tines remained outside. Further studies on the anatomy of a substantial number of human right atria (at necropsy) were performed. In conclusion it was considered unlikely that all tines could enter the right atrial appendage. This led to an increasingly more pronounced trimming of the tines (Fig. 1), a procedure which simplified the introduction of the lead into the vein as the untrimmed lead is relatively large. The lead function was not obviously impaired by the trimming.

Apart from the data obtained at insertion of the lead, the electrophysiological characteristics of the lead have not so far been reported. The acute P wave amplitudes obtained in the present study are by and large comparable with those obtained by other investigators using the same (Smyth *et al.*, 1976; Kleinert *et al.*, 1977) or different transvenous atrial leads (Rosenkranz and Schaldach, 1971; Cappelen and Hall, 1974; Furman *et al.*, 1977; Geddes *et al.*, 1978). The relatively minor differences may be explained by the technique of measuring especially as regards frequency response of the recording equipment (Citron *et al.*, 1978). The decrease in P wave amplitude which has been observed in the present material is of practical importance. Acceptance of a too low P wave may impose a risk of later loss of sensing. The input sensitivity of the atrial amplifier in the atrial synchronous and inhibited pacemakers available is usually about or somewhat below 1·0 mV. One of our patients had a P wave just less then 1·0 mV after one and four weeks and needed a pacemaker with a particular high P wave sensitivity. Taking the spontaneous P wave variability into consideration the importance of this decrease in P wave amplitude is still more underlined. On the assumption of an average 50 per cent decrease of the P wave amplitude from the level at insertion of the lead (average reduction 40% + spontaneous variability), the P wave should be well above 2 mV to be acceptable. In doubtful cases it is advisable to wait one week before final pacemaker implantation. At one week the P wave seems to reach the lowest level and a final decision can be taken about the choice of P wave sensitivity of the pacemaker. The present results also indicate that recording maximal and minimal P waves with the patient breathing normally and in the supine position should be sufficient when studying P wave variability. This can obviously be performed at the time of lead insertion since further changes are small. The cause of the decreasing P wave amplitude might be tissue reaction at the site of contact between the electrode tip and myocardium.

The threshold of stimulation of the right atrium was higher than that usually obtained in the right ventricle. The strength duration curves at the time of lead insertion are comparable to those reported previously (Smyth *et al.*, 1976; Kleinert *et al.*, 1977). The observed increase in pacing threshold was most pronounced during the first week after lead insertion and thereafter only a slight increase occurred. The increase was not statistically significant. This was probably related to the limited number of patients observed, and in absolute values the increase was not unimportant. The implication of this is that when necessary it will be possible to make a fairly accurate estimate of the final pacing threshold only one week after insertion of the lead. It should be emphasised that the J lead itself may never be exteriorised because of the risk of infection. A determination of the stimulation threshold and/or P wave amplitude should always be performed by means of a lead extension wire which, after subcutaneous passage, is externalised far away from the vein used for electrode insertion. An alternative way is to use pacemakers with a high P wave sensitivity or high output voltage in patients with low P waves or high thresholds of stimulation. However, we think these pacemakers should whenever possible be avoided because of an increased risk of electrical interference and a higher battery drainage.

Whether the P wave amplitudes and atrial stimulation thresholds observed at four weeks are stable or not remains to be investigated. It seems probable that further changes should at least be small as compared with those already established by that time because the greater part of the change appears to have occurred after one week. Furthermore, experience gained from ventricular pacing electrodes favours this belief (Siddons and Sowton, 1967).

The electrophysiological characteristics of the J shaped, tined atrial transvenous lead used in general are suitable for the available atrial synchronous and inhibited pacemakers. Clinical experience so far has been encouraging. However, there should be a larger number of patients and a longer follow-up, including long-term electrophysiology, before more definite conclusions can be made concerning the electrode. Thus this lead is qualified beyond any doubt for further use and may be the key to a justified increase in atrial synchronous and atrial inhibited pacing.

We thank Dr Richard Sutton for reviewing the manuscript.

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Case reports

British Heart Journal, 1979, **42**, 603-605

Pericardial effusion complicating psittacosis infection

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SUMMARY A 13-year-old schoolboy developed a moderately large pericardial effusion during the course of infection with psittacosis. The value of echocardiography in differentiating between pericardial effusion and myocarditis is shown.

Pericarditis complicating psittacosis infection is rare and to our knowledge no well-documented case of pericardial effusion caused by this infection has been described.

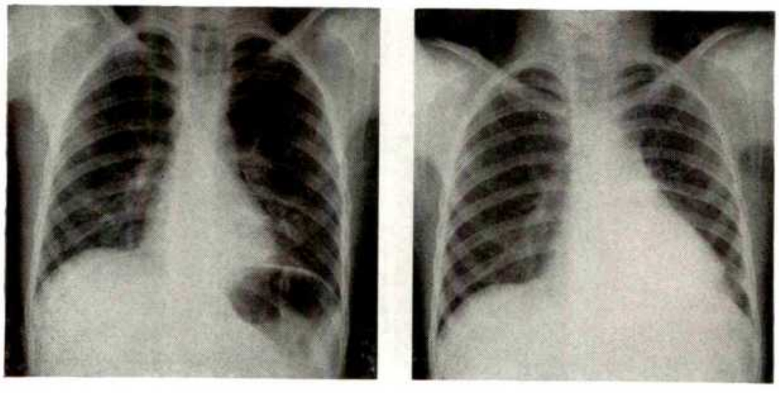
Case report

A 13-year-old schoolboy was admitted to hospital with a 2-day history of headache, left-sided chest pain, cough, and thick clear sputum. There had been no similar illness among his 5 brothers or 7 sisters. The poultry on the farm where he lived had not been diseased recently.

On examination he looked flushed, ill, and toxic, with a temperature of 39·2 °C, and a coated tongue. His respiratory rate was 20/minute and the pulse was 130/minute and regular. Blood pressure was 117/50 mmHg. There were expiratory rhonchi in both lower lobes. There were no abnormal heart sounds or murmurs and no friction rub was audible. There was no rash or lymphadenopathy.

The clinical diagnosis was bilateral bronchopneumonia. The chest *x*-ray film showed patchy inflammatory changes in both lower zones with a normal cardiac outline (Fig. 1a). The erythrocyte sedimentation rate was 54 mm in the first hour, Hb was 13·3 g/dl, and the white cell count 9 800 × $10^9/1$, with no neutrophilia. Sputum culture failed to grow bacterial pathogens. Acute viral studies showed normal antibody titres.

The patient was treated with ampicillin and cloxacillin to which oxytetracycline was added after 48 hours. The pyrexia subsided slowly and after 7 days these antibiotics were stopped. The pyrexia returned promptly and cotrimoxazole was started. At this time the erythrocyte sedimentation rate was 77 mm in the first hour and the Hb was 10·8 g/dl. Coombs' test was negative. A pericardial friction rub was audible and the electrocardiogram showed widespread ST and T wave changes consistent with pericarditis. A second chest *x*-ray film showed increase in the heart size, the contour suggesting pericardial effusion (Fig. 1b).



(a) (b)

Fig. 1 *(a) Chest* x-*ray film on admission. (b) Chest* x-*ray film showing pericardial effusion.*

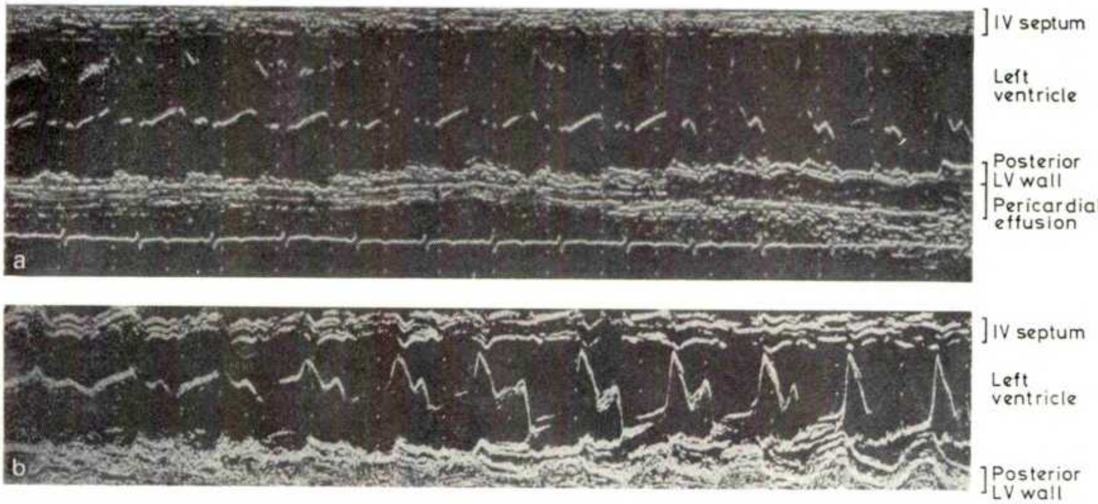


Fig. 2 (*a*) *Echocardiogram showing pericardial effusion.* (*b*) *Echocardiogram after resolution of effusion.*

The patient was transferred to the Cardiac Unit of the Belfast City Hospital where an echocardiogram confirmed the presence of a moderate pericardial effusion (Fig. 2a). The patient showed no signs of pericardial tamponade so pericardiocentesis was not performed. With bed rest the pericardial effusion resolved spontaneously. Four days later the echogram showed only a small amount of pericardial fluid. Two weeks after the onset of the illness the psittacosis/lymphogranuloma venereum complement-fixing antibody titre had risen from <10 on admission to 320.

The patient was transferred back to St. Columb's Hospital where a further chest *x*-ray film showed restoration of a normal cardiac contour, and complete resolution of the inflammatory changes in the lung fields. The erythrocyte sedimentation rate fell to 21 mm in the first hour. The Hb was 12·2 g/dl and the white cell count was $8\,400 \times 10^9/1$, with mild lymphocytosis.

The psittacosis antibody titre level remained 320 at the time of the patient's discharge from hospital 4 weeks after the onset of his illness, but had fallen to 40 one month later. Fourteen weeks after the onset of infection, the patient was clinically well and the electrocardiogram had returned to normal. The diameter of the cardiac shadow was at the upper limit of normal. The echocardiogram showed no pericardial fluid (Fig. 2b). The psittacosis antibody titre was 20.

Discussion

Psittacosis in humans usually affects the respiratory system, the mode of infection being by inhalation. Isolated cases of cardiac involvement have been reported, usually taking the form of myocarditis (Coll and Horner, 1967; Dymock *et al.*, 1971). Clinical evidence of pericarditis is rare. Definite clinical and serological evidence of psittacosis was found in only 3 out of 599 unselected cases of acute perimyocarditis reported by Sutton *et al.* (1967).

In the present case the diagnosis of acute psittacosis infection was established by the clinical features and the typical acute rise and fall in complement fixing antibody titre to psittacosis–LGV agent. There were no clinical signs of lymphogranuloma venereum. The source of infection remains unclear. The patient was responsible for cleaning out the chicken house weekly on the farm where he lived and would sometimes find a dead chicken there. However examination of the flock subsequently by a veterinary surgeon was negative for psittacosis. Grist and McLean (1964) reported 16 cases in whom there was no obvious source of infection.

The development of a substantial pericardial effusion, which was the most noteworthy aspect of this case, was established conclusively by the typical radiological and echocardiographic findings. In another case in which a pericardial effusion was suspected during life, necropsy showed only a little pericardial fluid and that most of the increase in the diameter of the cardiac shadow was the result of severe myocarditis (Dymock *et al.*, 1971). The value of echocardiography in differentiating between myocarditis and pericardial effusion was seen well in the present case. It is surprising that pericardial effusion has not been described more frequently in human psittacosis. In birds it is one of the commonest findings (Yow *et al.*, 1959). The increasing availability of echocardiography may show that small effusions are commoner than has been believed.

The relatively slow fall in the patient's temperature despite vigorous treatment with oxytetracycline, and the secondary rise in temperature after discontinuing this drug may have been because of difficulty in eradicating the infection from the pericardial effusion. The demonstration of such effusions and their differentiation from myocarditis may be useful in estimating the prognosis of patients with cardiac involvement in psittacosis. This patient's full recovery from a pericardial effusion stands in distinct contrast to the fatal outcome from myocarditis in the cases described by Dymock *et al.* (1971) and Vosti and Roffwarg (1961).

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British Heart Journal, 1979, **42**, 606–607

Aortic regurgitation in newborn

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SUMMARY Clinical signs of aortic regurgitation were noted after birth in an infant who died suddenly at the age of 18 months. Congenital malformation of the aortic root with an aneurysm of the right aortic sinus and disconnection of the corresponding cusp were found at necropsy.

Aortic regurgitation occurs in infancy or later usually as the result of congential malformations of the aortic root or rheumatic disease of the aortic cusps. We have recently observed an infant who died at age 18 months with a congenital malformation of the aortic root presenting as aortic regurgitation from birth. The case reported here appears to be unique.

Case report

The patient was a full-term female baby, birth weight 3750 g. Pregnancy and family history were uneventful. Physical examination soon after birth showed no abnormality except those of the cardiovascular system. No features of Marfan's or other connective tissue disorders were present. Auscultation revealed a to-and-fro murmur, grade 4/6, with maximal intensity along the left sternal edge; phonocardiography showed that the murmur consisted of a systolic ejection and an early diastolic regurgitant component. Brachial and femoral pulses were of bounding quality.

Electrocardiogram showed sinus tachycardia and severe left ventricular hypertrophy.

Chest *x*-ray film disclosed pronounced enlargement of the cardiac shadow.

Cardiac catheterisation and angiography under general anaesthesia at the age of 1 month showed that pressures in the right atrium, left atrium, right ventricle, pulmonary artery, and left ventricle (entered through a patent foramen ovale) were, respectively (−1), (4), 25/0, 18/7, 78/0/8 mmHg. There was no difference in oxygen saturation between the right atrium and the pulmonary artery. Arterial saturation was normal.

Left ventriculography showed moderate enlargement of the left ventricular cavity with considerable thickening of the left ventricular walls. The aorta was dextroposed and its ascending portion and arch much enlarged. At the level of the aortic ring an aneurysm the size of a nut was observed and was thought to originate from the right aortic sinus (Fig. 1). Coronary arteries were thin; pseudocoarctation of the aortic isthmus was suspected.

The infant was digitalised and subsequent clinical course was characterised by slow weight

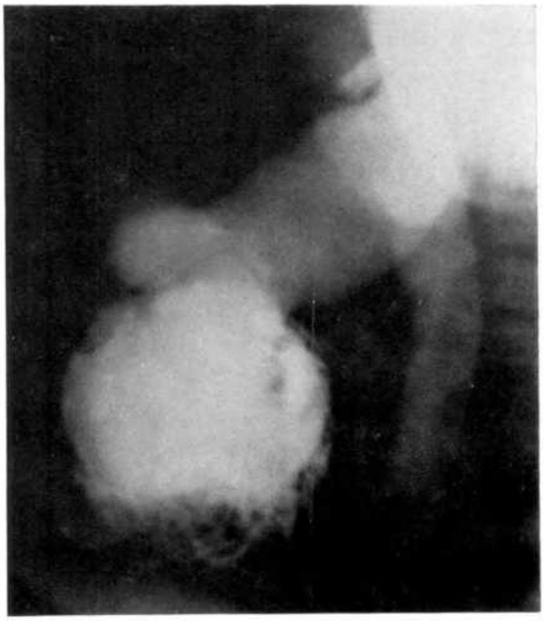

Fig. 1 *Left ventriculography lateral view.*

gain (8 kg before death), difficulties in feeding, and tachycardia. Cardiovascular findings remained unchanged throughout her life. Recatheterisation and surgical repair of the defect were planned but the patient died suddenly at the age of 1½ years.

NECROPSY FINDINGS

The heart weighed 110 g. Cardiomegaly was the result principally of hypertrophy of the left ventricular wall. The right ventricle was hypoplastic. The pericardial surfaces of the heart were normal. The left anterior and the posterior non-coronary aortic cusps were normal, while the right anterior cusp was not connected for one-half of its base to the aortic ring (Fig. 2). The corresponding aortic Valsalva sinus was aneurysmal. The aneurysm was 10×7 mm, not ruptured, and protruded into the right ventricular cavity. There was no suggestion of recent or old bacterial endocarditis.

Histological examination of aortic sinus aneurysm disclosed the presence of connective collagen tissue without evidence of inflammation. The aortic wall showed no signs of cystic medial necrosis and several myocardial sections showed only distinct hypertrophy of muscular fibres.

Discussion

Congenital malformation of the aortic root usually consists of aneurysm of the Valsalva sinuses while semilunar cusps may be fenestrated or bicuspid. Clinical manifestations ensue in infancy or later when the malformed structures either rupture or became fibrotic and calcific. In the present case a congenitally weak junction of the heart and the aorta, which is usually responsible for aneurysm of the aortic sinus, probably led to failure of connection of the right aortic cusp to the aortic ring (Fig. 2). The latter was in turn responsible for the aortic regurgitation present at birth, as the aneurysm of the corresponding aortic sinus was found to be intact both at angiography (Fig. 1) and at necropsy. The cause of the fetal malformation remains unknown.

Clinically, aortic regurgitation should be considered in the differential diagnosis of a bounding pulse and to-and-fro murmur in an infant.

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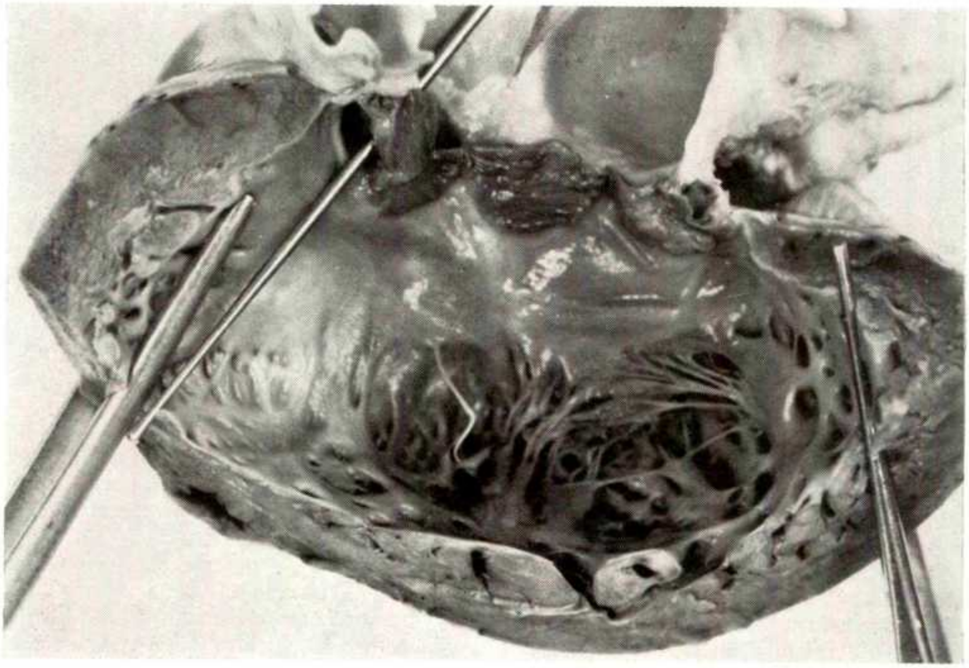

Fig. 2 *Necropsy specimen showing a probe passing through the base of the right aortic cusp into the ascending aorta. The aneurysm of the aortic cusp is located just behind and below that portion of the aortic ring which has no connection with the cusp.*

British Heart Journal, 1979, **42**, 608-610

Calcified left atrial myxoma with floppy mitral valve

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SUMMARY A heavily calcified left atrial myxoma in a man aged 53 was diagnosed from the plain chest *x*-ray film and confirmed by echocardiography. There was also moderate mitral regurgitation caused by a floppy mitral valve. Before a systemic embolus is considered to have arisen from a floppy mitral valve, echocardiography must be performed.

Myxomata of the left atrium usually present with the features of mitral valve obstruction, systemic emboli, or constitutional symptoms (Goodwin, 1963). Mitral regurgitation is a rare presenting feature (Penny *et al.*, 1967). We report the case of a patient who presented with cerebral embolism and the signs of mitral regurgitation, in whom a calcified left atrial myxoma was found by *x*-ray film and echocardiography.

Case report

A 53-year-old man was referred for consideration of mitral valve replacement for mitral regurgitation. He was thought to have had rheumatic fever as a child and mitral murmurs had been present for at least 20 years. He was seen by a physician in 1971 for dyspepsia and was thought to have mitral regurgitation. He was then in sinus rhythm. Three months before admission to this unit he had been admitted elsewhere with a right hemiparesis which was thought to be caused by a cerebral embolus associated with the onset of atrial fibrillation. He had made a complete neurological recovery but complained of dyspnoea on moderate effort.

On examination there was atrial fibrillation, all the peripheral pulses were present and normal, blood pressure 140/80 mmHg. The jugular venous pressure and pulse were normal. There was a moderately increased, dynamic, left ventricular impulse palpable at the anterior axillary line. A grade 2/4 apical pansystolic murmur with late crescendo radiated to the axilla. There was a soft short mitral diastolic murmur. The electrocardiogram confirmed atrial fibrillation and showed unifocal ventricular extrasystoles. The chest *x*-ray film (Fig. 1) showed a calcified mass within the left atrium. A diagnosis of a moderate mitral regurgitation with a calcified left atrial myxoma or thrombus was made. Echocardiography (Fig. 2a and 2b) suggested mitral valve prolapse and confirmed a dense mass in the left atrium which did not pass through the mitral valve in diastole. The haemoglobin was 15·1 g/dl and the white blood cell count, platelets, and plasma proteins were normal. The ESR was 33 mm in one hour.

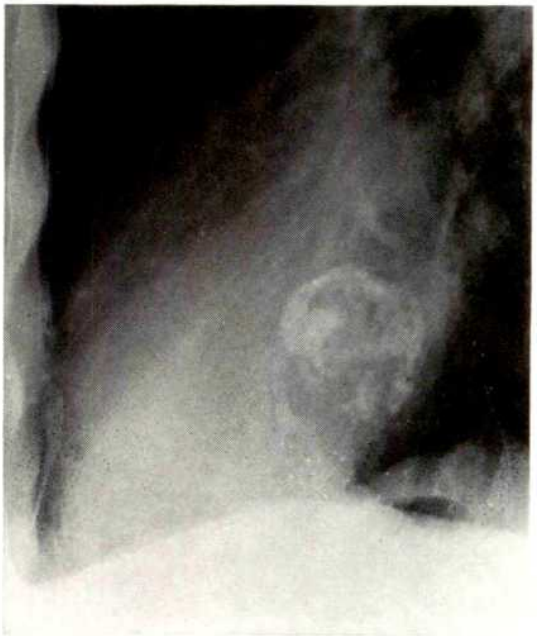

Fig. 1 *Plain lateral chest* x-ray *film showing a calcified mass in the region of the left atrium.*

Operation was performed without further investigation. The left atrium was found to contain a hard smooth, yellowish tumour measuring 5 cm by 2·5 cm. The mass was attached by a short pedicle to the posterior left atrial wall just below and medial to the right inferior pulmonary vein and 2 cm from the mitral valve. It was excised, together with its

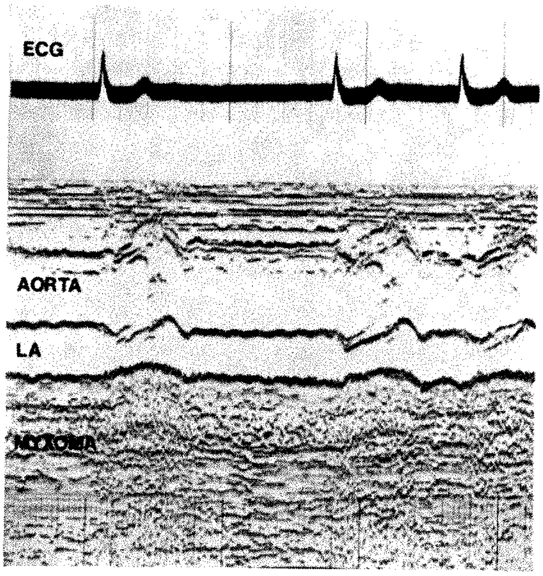

Fig. 2(a)

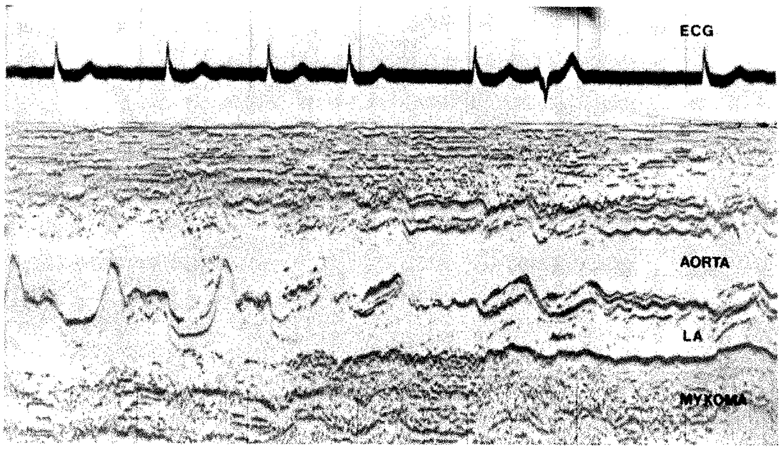

Fig. 2(b)

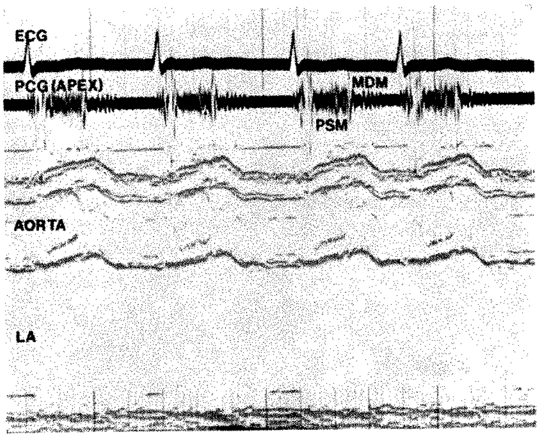

Fig. 2(c)

Fig. 2 (a) *Echocardiogram of the aorta and left atrium (LA) showing a mass of echoes in the left atrium caused by the myxoma.* (b) *Echocardiographic sweep from the mitral valve to the aorta and left atrium. The echo mass does not prolapse through the mitral valve. There appears to be pansystolic prolapse of the mitral valve.* (c) *Echocardiogram of the aorta and left atrium. The left atrium is now echo free but enlarged to 5 cm. The apical phonocardiogram (PCG) shows a pansystolic murmur (PSM) with late systolic crescendo, and a mitral diastolic murmur (MDM).*

pedicle and the related disc of atrial wall. The mitral valve appeared to be of the floppy type, and on testing was thought to be only mildly regurgitant and was therefore not replaced.

Postoperative recovery was uneventful. He continued to have signs of moderate mitral regurgitation, and echocardiography (Fig. 2c) confirmed that the left atrium was now echo free but enlarged. He was asymptomatic.

Histology of the mass showed the typical features of an atrial myxoma, with calcification.

Discussion

Atrial myxomata, once considered to be extremely rare, are now being diagnosed with increasing frequency. Greenwood (1968) reported an incidence of 1 in 200 to 400 operations for mitral valve obstruction. The Wessex Cardiothoracic Centre serves a population of 2·7 million people that may be considered to show a representative distribution of cardiac diseases (Ross *et al.*, 1976). In the past 5 years we have seen 7 atrial myxomata and in the same period have performed 502 operations for isolated mitral valve disease on cardiopulmonary bypass.

Heavy calcification of atrial myxomata is uncommon and appears to be more frequent when the tumour is in the right atrium (Krcilkova *et al.*, 1958; Wight *et al.*, 1963; Oliver and Missen, 1966; Fluck and Lopez-Bescos, 1968; Fleming and Stoven, 1972) rather than in the left atrium (Wight *et al.*, 1963; Penny *et al.*, 1967). In this case the calcification was heavy enough to allow a diagnosis to be made from the lateral chest *x*-ray film.

The mitral valve (Nasser *et al.*, 1972) or aortic valve (Rose *et al.*, 1974) may become regurgitant because of damage from tumour motion. In this case mitral valve prolapse appeared to be the cause of the mitral regurgitation and at surgery the appearances were those of a floppy mitral valve. Rheumatic mitral disease has been reported in association with left atrial myxoma (Marions and Ödman, 1957; Aldridge and Greenwood, 1960), but we are not aware of any previous report of left atrial myxoma coexisting with floppy mitral valve.

Systemic emboli have been reported as a complication of the floppy mitral valve (Wilson *et al.*, 1977). In the case here reported it is not possible to know whether this, the myxoma, or the atrial fibrillation was the cause of the embolism but it does illustrate that echocardiography should always be performed before other cardiac lesions are accepted as being the cause of systemic embolism.

We thank Dr A. M. Johnson for permission to publish this case, and for advice in the preparation of the manuscript.

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Asymmetric septal hypertrophy and propranolol treatment in a case of Ullrich-Noonan syndrome

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SUMMARY A 4-year-old boy with the Ullrich-Noonan syndrome is described. Asymmetric septal hypertrophy was diagnosed by echocardiography and confirmed at cardiac catheterisation. The aortic subvalvar gradient was reduced from 56 mmHg to 10 mmHg with intravenous propranolol. Relatives of patients with the syndrome should be screened by echocardiography in the hope that the early detection of asymmetric septal hypertrophy and its treatment with propranolol may reduce the likelihood of sudden death.

The clinical and cardiovascular manifestations in patients with the Ullrich-Noonan syndrome have been extensively reviewed (Nora *et al.*, 1974). Patients, who may be of either sex, have a normal karyotype, but have an appearance typical of Turner's syndrome, very short stature, webbing of the neck, and a typical facies. The most common cardiac abnormality is valvar pulmonary stenosis with or without an atrial septal defect. Less frequently, stenosis of the peripheral branches of the pulmonary arteries, aortic stenosis, ventricular septal defect, the tetralogy of Fallot, persistent ductus arteriosus, and coarctation of the aorta may occur. Asymmetric septal hypertrophy (ASH) has been reported more recently (Ehlers *et al.*, 1972). Nora *et al.* (1974) reported 2 cases of isolated ASH, 5 associated with pulmonary stenosis, and 1 associated with coarctation of the aorta. Phornphutkul *et al.* (1973) reported 1 case of ASH and 2 cases of non-obstructive cardiomyopathy. Here we report a further example of the syndrome in whom the cardiac abnormalities were ASH and aortic stenosis.

Case report

A 4-year-old white boy with a clinical diagnosis of the Ullrich-Noonan syndrome was referred for cardiological investigation. His mother had been previously diagnosed at another hospital as having the Ullrich-Noonan syndrome associated with ASH. She had recently died as a result of accidental electrocution. Three of the mother's sibs had heart disease. One died when 2 hours old, one died aged 3 weeks, and one had an aortic valve replacement for aortic stenosis when aged 38. The cause of death of the youngest 2 was given as congenital heart disease. Our patient has a co-maternal half sister who is cardiologically normal.

Our patient complained of slight shortness of breath on vigorous exercise but was otherwise asymptomatic. His milestones were normal and he was not mentally retarded. His height was below the third centile and his weight was at the fiftieth centile. He had a small mouth, broad nose, widely spaced eyes, a left epicanthic fold, and slight right ptosis. He had prominent, low set ears and a low hairline at the neck. There was no webbing of the neck or pectus excavatum. His right testis was not fully descended. Cardiac examination revealed a normal heart size with a left ventricular impulse, a late systolic murmur maximal at the left sternal edge and a fourth heart sound. His buccal smear was chromatin negative and he had a normal male karyotype. His electrocardiogram showed a mean frontal plane axis of minus 110 degrees with large R waves in leads aVR and aVL and a QS pattern in lead V6 with a deep Q wave in V5 (Fig. 1). Chest *x*-ray film was normal. An echocardiogram (Fig. 2) disclosed septal hypertrophy, the septal thickness being 1·3 cm just below the level of the mitral valve. There was systolic anterior movement of the mitral valve and the anterior leaflet of the mitral valve impinged upon the septum in diastole. The pressures recorded at cardiac catheterisation are shown in the Table, the left ventricular end-diastolic pressure being 12 mmHg with a gradient of 56 mmHg within the left ventricle and an aortic

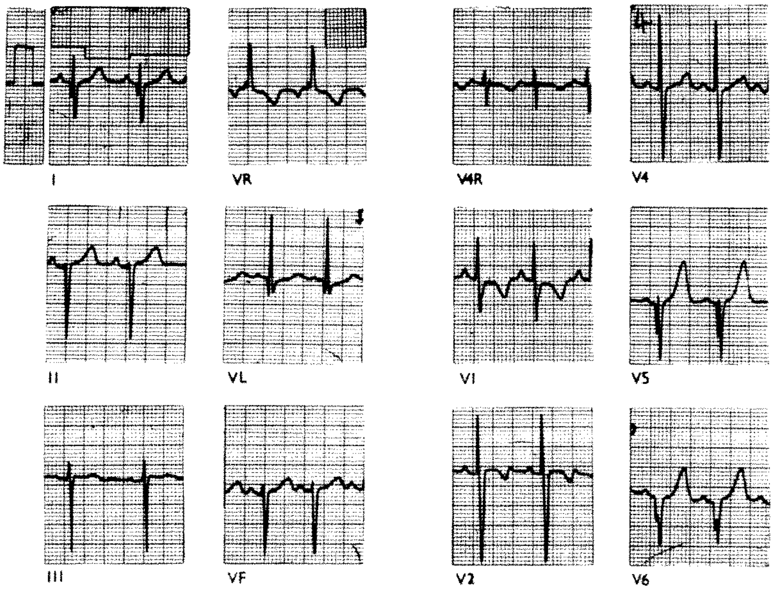

Fig. 1 *Electrocardiogram (paper speed 25 mm/s). See text.*

valvar gradient of 44 mmHg. Though the foramen ovale was crossed, measurement of oxygen saturation did not reveal any arteriovenous shunt. The absence of an intra-aortic pressure gradient excluded coarctation. No pressure gradient was found in any branch of the pulmonary arteries.

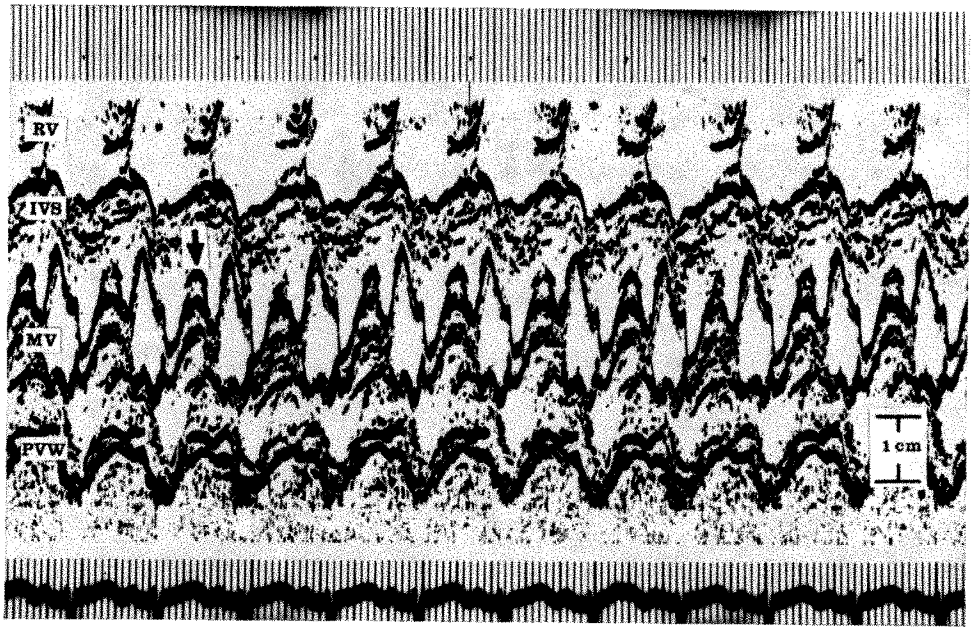

Fig. 2 *M-mode echocardiogram (paper speed 50 mm/s) at the level of the anterior leaflet of the mitral valve. There is prominent systolic anterior movement of the anterior leaflet which has a reduced diastolic closure rate and abuts on to the septum in diastole. RV, right ventricle; IVS, interventricular septum; MV, mitral valve; PVW, posterior ventricular wall.*

Table *Pressures recorded at cardiac catheterisation (mmHg)*

Right atrium	8 mean	Aorta	100/64
Right ventricle	28/0	Left ventricle	200/12
Pulmonary artery	28/10	Left ventricle (after propranolol)	144/12
Pulmonary artery branches	28/10	Subvalvar gradient	56
Left atrium	8 mean	Aortic valvar gradient	44

Left ventricular angiography showed septal hypertrophy, trabeculation, and mitral regurgitation (Fig. 3). After the administration of propranolol 0·8 mg (0·05 mg/kg) intravenously, the subvalvar gradient was reduced to 8 mmHg, with the aortic valvar gradient also being reduced to 10 mmHg. Biopsy of the right ventricle was histologically normal; biopsy of the left ventricle was technically unsuccessful. The patient was discharged home taking propranolol 5 mg t.d.s. Three weeks later the patient was asymptomatic and his murmur had decreased in intensity. The echocardiogram was repeated 3 months later, propranolol having been withdrawn for 48 hours. The degree of systolic anterior movement of the mitral valve was less than that of the control recording despite temporary withdrawal of treatment. The administration of propranolol 0·8 mg intravenously produced a further slight reduction in systolic anterior movement.

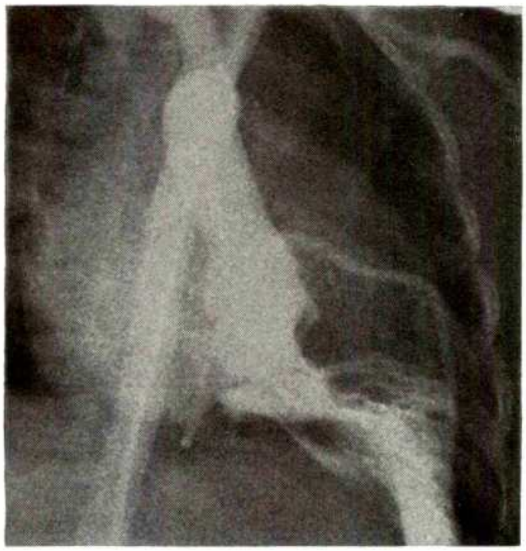

Fig. 3 *Left ventricular angiogram in the right anterior oblique position illustrating severe septal hypertrophy and mitral regurgitation.*

Discussion

We report a case of the Ullrich-Noonan syndrome associated with ASH investigated by echocardiography, left and right heart catheterisation, and right ventricular biopsy. The proven concurrence of ASH with the Ullrich-Noonan syndrome in the mother of our patient strongly suggests that his ASH was inherited as a manifestation of this syndrome.

The reduction of the outflow tract gradient achieved with propranolol in this patient is similar to that found in isolated ASH (Goodwin and Oakley, 1972). The echocardiographic findings were typical of ASH. It is of interest to note that the extent of the systolic anterior movement, and hence the outflow gradient, was reduced after treatment with propranolol for three months despite temporary withdrawal of the drug.

It has been suggested that a superior frontal plane QRS axis in the Ullrich-Noonan syndrome indicates pulmonary stenosis (Rasmussen and Sørland, 1973). We found such an axis but no pulmonary stenosis. However, the presence of a QS pattern in lead V6 and an R wave in lead aVL is compatible with ASH (Bahl and Massie, 1972).

Septal hypertrophy has not been the most frequent association with the Ullrich-Noonan syndrome in the patients so far reported, but since many of these have been investigated only by right heart catheterisation ASH would not necessarily have been suspected. It is possible that the pulmonary stenosis reported in some patients may have resulted from a gradient in the outflow tract of the right ventricle caused by septal hypertrophy. The exact incidence of ASH among patients with the syndrome, and their families can be conveniently determined by echocardiography. It may be that ASH is the common denominator in a group of genetically determined disorders, of which the Ullrich-Noonan syndrome is one.

We have shown a favourable haemodynamic and symptomatic response to propranolol in a patient with the Ullrich-Noonan syndrome. The echocardiographic examination of similar patients and their relatives may lead to early diagnosis of ASH. Treatment with propranolol may in turn favourably affect the natural history of affected individuals, perhaps even reducing the incidence of sudden death, as the presence of congenital heart disease significantly affects mortality (Nora *et al.*, 1974).

We would like to thank Dr P. R. Clay for referring this patient to us.

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British Heart Journal, 1979, **42,** 615–616

Right ventricular monophasic action potentials in patients with long QT syndrome

Sir,

Gavrilescu and Luca in their recent paper (*British Heart Journal,* 1978, **40,** 1014–1018) have reported different patterns of ventricular monophasic action potential recorded in patients with long QT syndrome. On the basis of their observations they conclude that ventricular arrhythmias in those patients may be triggered by critical differences of refractoriness between various ventricular areas resulting from uneven and delayed repolarisation of ventricular myocardium. A close analysis of their right ventricular monophasic action potential tracings suggests the following.

(1) The different morphological configuration of the right ventricular monophasic action potential shown in Fig. 5 (A) and Fig. 5 (B) suggests that the 2 recordings were obtained from different types of ventricular fibres. The former (A) with an obvious plateau, from Purkinje fibres; the latter (B) from contractile myocardium. This should, at least in part, account for the wide difference in monophasic action potential duration (Fenici *et al.,* 1978b).

(2) I agree that the so-called 'second monophasic action potential deflections' (0_1—Fig. 4 (C) and Fig. 5 (C)) are not artefacts but I think that they could be interpreted as afterpotentials rather than as delayed repolarisations, especially as their amplitude

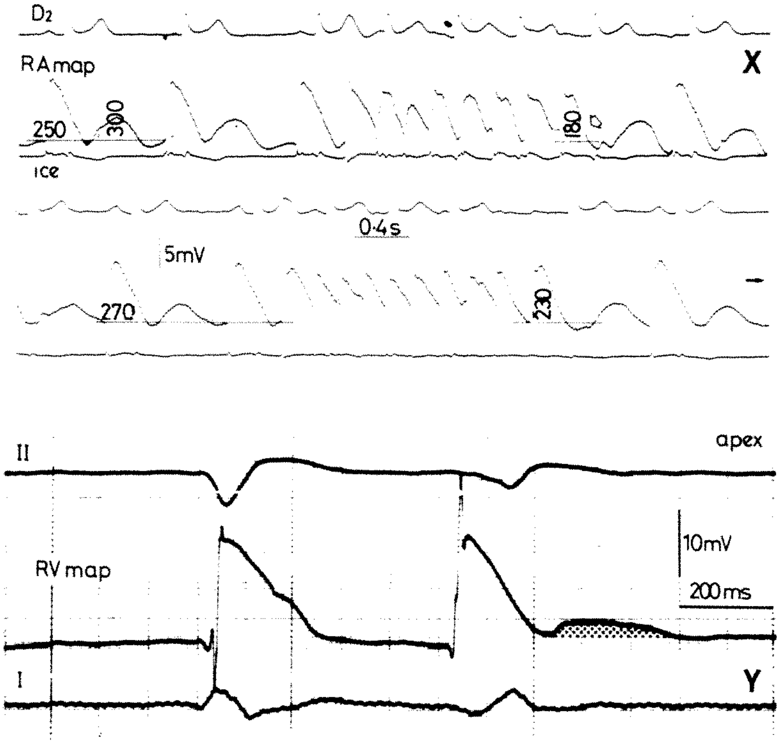

Fig. *Examples of 'after-potentials' recorded: at atrial level* (X), *a patient with paroxysmal atrial fibrillation; and at ventricular level* (Y), *patient with massive digoxin intoxication.*

increased with decreasing cycle length (Cranefield, 1977). This might suggest 'triggered activity' rather than re-entry as the most reasonable mechanism of the onset of ventricular arrhythmias in that patient. Similar diastolic phenomena have been recorded by me in a patient with paroxysmal atrial fibrillation (Fenici *et al.*, 1978a) and another with severe digoxin intoxication (Fenici *et al.*, 1978c). In both cases arrhythmias appeared to be triggered, either spontaneously or electrically, from the ascending phase of the 'afterpotentials' (see Fig.).

(3) Monophasic action potential recording in case 3 shows also that QT intervals of the same duration may be explained either by the duration of the action potential of 'plateau' fibres (Fig. 5 (A)), or by the occurrence of 'early' afterpotentials (Fig. 5 (C)). This suggests that further investigations by monophasic action potential recording technique could prove to be useful in clarifying the electrophysiological mechanism underlying the genesis of the U wave which is at present still controversial (Hoffman and Cranefield, 1960).

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Hoffman, B. F., and Cranefield, P. F. (1960). *Electrophysiology of the Heart,* pp. 201–202. McGraw-Hill, New York.

This letter was shown to Drs Gavrilescu and Luca who reply as follows.

Sir,

We are grateful to Dr Fenici for his pertinent observations. However, we must reiterate our belief that the method of monophasic action potential recording in the intact heart has many limitations so that conclusions drawn by using this method alone are often speculative. It is true that different morphological right ventricular monophasic action potential configurations can be the result of recording from various anatomical structures, but in our experience with normal and pathological hearts both in man and animals we have never encountered these differences, with the exception of the long QT syndrome. On the other hand, such a configuration can change, as in case 1, simultaneously with the regression of the prolonged QT interval. We can not exclude the explanation forwarded by Dr Fenici concerning the configuration of monophasic action potential recordings shown in Fig. 4 (C) and Fig. 5 (C). However, we believe that the prolonged refractoriness found with the help of pacing is more likely to be the result of prolonged repolarisation. We agree that some modifications of the T wave and of the U wave may be clarified by using monophasic action potential recordings.

S. Gavrilescu and C. Luca,
Department of Internal Medicine
and Cardiology, Institute of
Medicine, Timisoara, Romania.

British Heart Journal, 1979, **42**, 617-618

Glyceryl trinitrate before coronary angiography

Sir,

The factual information in a recent publication by Dr Feldman *et al.* (Feldman, R. L., Pepine, C. J., Curry, R. C., Conti, C. R., 1978, *British Heart Journal*, **40**, 992–997) is an excellent contribution, I am concerned that the conclusions are philosophical and deviate from the practical aspects of evaluation of patients with suspected coronary artery abnormalities.

Abnormality implies deviation from the normal. Glyceryl trinitrate has been shown usually to dilate vasoactive coronary arteries from the diameter present before therapy. What is normal? Is the coronary artery calibre of an unpremedicated patient in an unfamiliar room, whose body is being 'invaded', more normal than the coronary artery calibre of a sedated, vasodilated patient?

Is the accuracy of measurement of a narrowed vessel with normal (or possibly enhanced) vasomotor tone as reproducible as in a dilated vessel?

Which measurement of narrowing or fixed obstruction with or without dilators and/or sedation would correlate best with clinical symptoms, operative findings, lactate abnormalities, or ventriculographic abnormalities?

My clinical impression is that the sedated, vasodilated patient can be accurately studied. The angiographic data are reliable guides to clinical status and operative intervention. Evaluation of the noncoronary dilated patient is of great value in scientific evaluation. Nevertheless, the withholding of coronary dilators will cause referrals for coronary artery bypass surgery of normal arteries that are vasoconstricted. The differentiation between organic and functional narrowing is never easy.

If coronary angiography is performed without coronary vasodilators, it should be repeated during the same study after adequate coronary vasodilatation.

Richard L. Coskey,
Cardiology Consultants Medical
Group Inc.,
18370 Burbank Boulevard, Suite 707,
Tarzana, California 91356, USA.

This letter was shown to Dr Feldman and his co-authors who reply as follows:

Sir,

First, we agree that it is difficult to know what is 'normal' with regard to coronary artery size and narrowing. To our knowledge, no one has specifically reported the influence of sedation on coronary artery diameters in man.

Secondly, in our experience, we have found that 'accuracy' of measurements of narrowed vessels of patients with presumably 'normal' vasomotor tone (i.e. without Prinzmetal's angina) are as reproducible as measurements made in vessels dilated by glyceryl trinitrate (Feldman *et al.*, 1979a). Our recent studies suggest that if measurements are made using a high-quality angiography system with an optical measuring device, a very high level of accuracy is achieved (Feldman *et al.*, 1979a, b). This level of accuracy (94 to 96%) probably represents the maximum possible with current angiographic systems.

Thirdly, there are no data that we are aware of, to relate symptoms, operative findings, lactate abnormalities, or ventriculographic abnormalities with measurements of fixed obstructions with and without coronary dilators or sedation. We can only speculate that the size of coronary arteries in the absence of drugs would correlate best with symptoms, etc.

Finally, we emphasise that the comment that the sedated vasodilated patient can be 'accurately' studied is only Dr Coskey's impression. Since signs and symptons of ischaemia occur only infrequently in sedated vasodilated patients, we take the view that angiographic and haemodynamic data are possibly distorted and do not reliably represent the patient's clinical status. We do not agree that evaluation of the non-coronary dilated patient is only of scientific value. In sedated patients or anaesthetised animals, glyceryl trinitrate (Gensini *et al.*, 1971) clearly increases the diameter of normal coronary artery segments. If a patient is studied only after glyceryl trinitrate, the investigator might miss an unexpected case of coronary spasm. Laboratories that routinely use sedation and vasodilators rarely report seeing coronary spasm in contrast to those laboratories that do not use these agents before angiography (Bennett, 1976). In addition, infrequently, a 'paradoxical response' to glyceryl trinitrate is observed (Feldman *et al.*, 1978), and Fig. 4, *British Heart Journal*, 1978, **40,** 992–997). We are unaware of published data to support Dr Coskey's contention that withholding coronary dilators causes referrals for bypass surgery of normal arteries. None the less, we emphasised in our manuscript that routine coronary angiograms should be performed before and after glyceryl trinitrate. We are not alone in this recommendation (Chahine and Luchi, 1976).

Robert L. Feldman, Carl J. Pepine,
R. Charles Curry and C. Richard Conti

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British Heart Journal, 1979, **42**, 619

A severe complication of pulmonary vein angiography

Sir,
Recently (Alpert, B. S., and Culham, J. A. G., 1979, *British Heart Journal*, **41**, 727–729), we reported a near-fatal complication of a pressure injection pulmonary venous angiogram. We suggested that extravasation might be avoided by the use of an end-hole catheter in the wedge position, slow flow rate of contrast, and low-pressure injection. Since our initial experience with a pressure injection, we have used end-hole balloon catheters exclusively. We have used 0·3 to 0·4 ml per kg contrast at a flow rate of 2 ml/s. The pressures achieved have not exceeded 300 psi. Despite these precautions and generally excellent results, we have again produced an extensive extravasation in one of our smaller patients, a 4·4 kg 4-month-old boy. In this patient, contrast medium appeared also in both main bronchi.

Although we do not know the pressure required to rupture a pulmonary capillary or venous bed, we suggest that even at slow flow rates (2 ml/s) critical pressure may be exceeded when the cross-sectional area of the vascular bed subtended is small. At present we are trying to evaluate the use of graded flow rates with lower flow rates in smaller patients. Ideally, we would like to be able to recommend a flow rate which allows diagnostic visualisation but does not produce life-threatening complications. As yet, we do not have enough data to do so.

Bruce S. Alpert,[1]
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Department of Paediatrics,
and J. A. Gordon Culham,
Department of Radiology,
The Hospital for Sick Children,
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[1] Supported by the Ontario Heart Foundation.

Notice

British Heart Journal, 1979, **42**, 620

Bulletin of the European Society of Cardiology

As a result of widespread discussions, the Board of the European Society of Cardiology has decided to publish its own scientific journal and this will be called *The European Heart Journal.*

Its Editor-in-Chief will be Professor Desmond Julian, whose address is Department of Medicine (Cardiology), The University of Newcastle upon Tyne, Freeman Hospital, Newcastle upon Tyne NE7 7DN. The publishers will be Academic Press.

The Journal will start publication at the beginning of 1980 and initially will be issued every two months.

It is intended that this should be an international journal of the highest scientific standards and that it will, in addition, provide a special forum for European cardiology and will facilitate the diffusion of information from the European Society to its members.

It is planned to offer the Journal to members of all National Cardiological Societies in Europe at a reduced rate.

For further information and inquiries concerning the submission of manuscripts, please write to: Academic Press Inc. (London) Limited, 24–28 Oval Road, London NW1 7DX. *For the attention of:* Mr R. A. Farrand.

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Contributors should note that, in future, references in the text of papers submitted to this journal and in the bibliography should be prepared in the new format, as outlined briefly in the Notice to contributors.

Full details of this new, uniform style, which was agreed at a meeting of the International Steering Committee of Medical Editors held in Vancouver, were published in the *Br Med J* (1979; **1**: 532–35) and *Ann Intern Med* (1979; **90**: 95–9). Reprints of this article are available from the *Br Med J* (price 50p).

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Am. J. Cardiol. (1977) **39,** 91. Bussmann WF et al : Orally administered isosorbide dinitrate in patients with and without left ventricular failure due to acute myocardial infarction.

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Am. J. Cardiol. (1977) **39,** 84. Williams DO et al : Hemodynamic assessment of oral peripheral vasodilator therapy in congestive heart failure : prolonged effect of isosorbide dinitrate.

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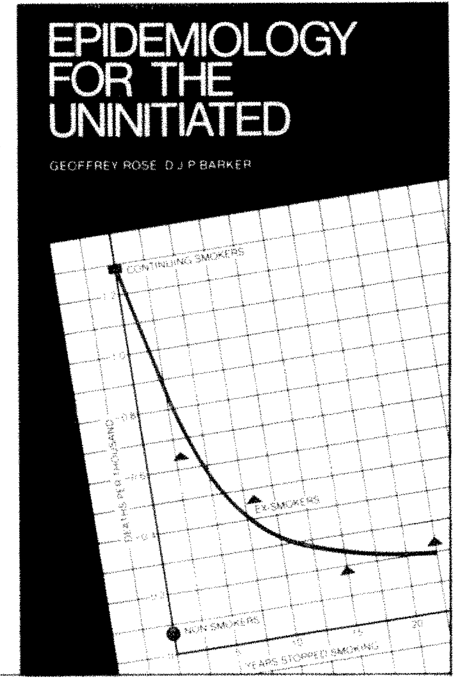

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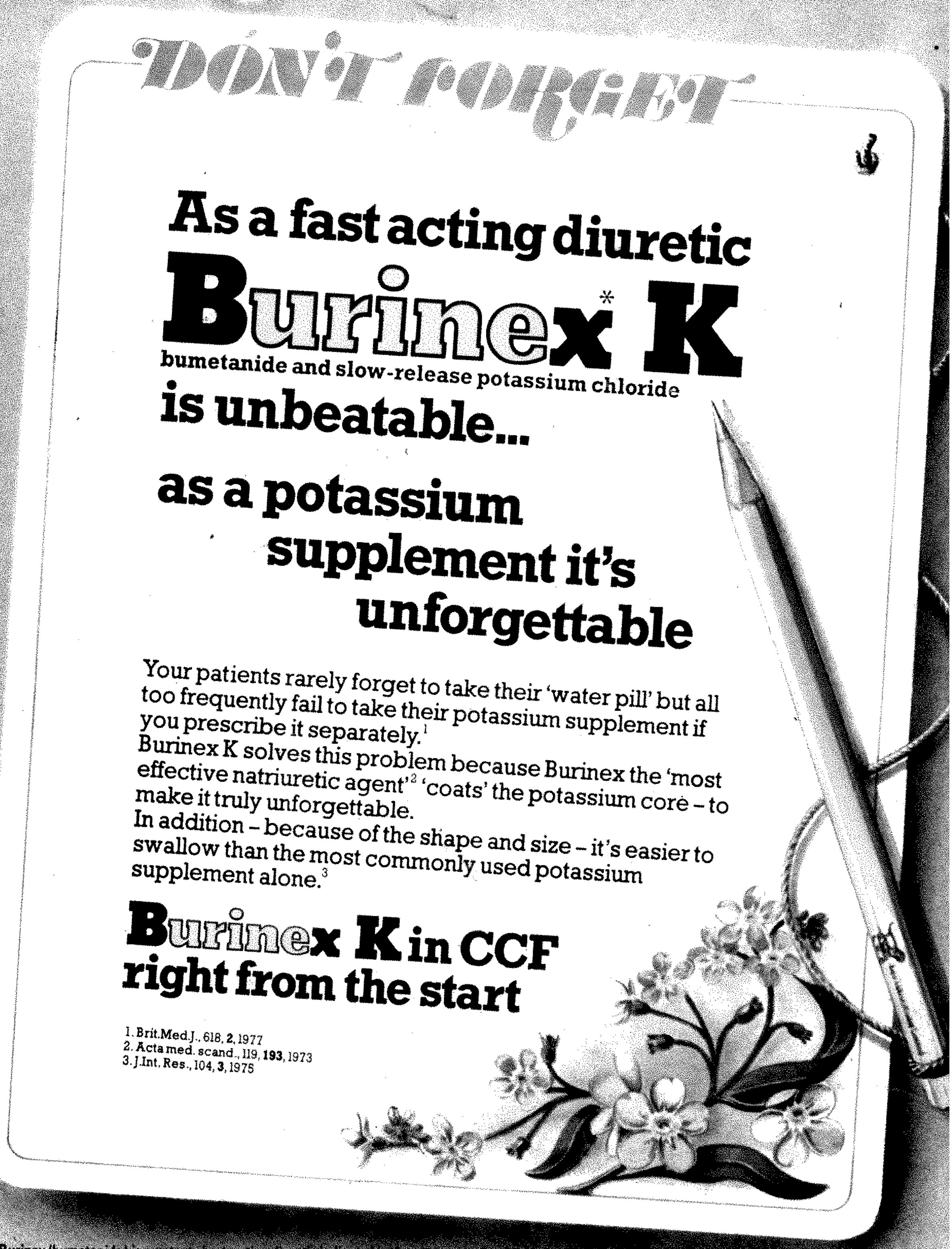

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(1) *Standard journal article*—(List all authors when six or less; when seven or more, list only first three and add *et al.*):
Walmsley R. Anatomy of left ventricular outflow tract. *Br Heart J* 1979;**41**:263–67.

(2) *Books and other monographs:*
Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology 1977.* Edinburgh, London: Churchill Livingstone, 1978: 16–26.

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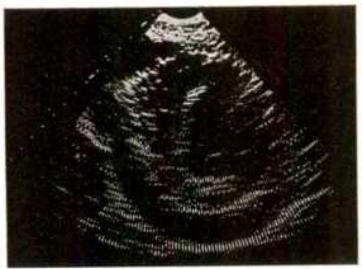
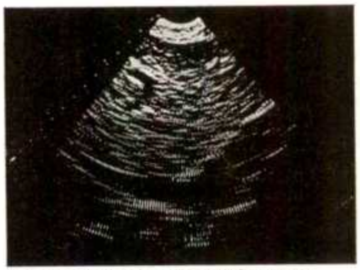


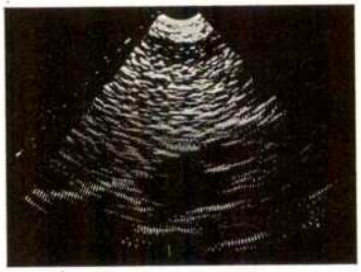
Left ventricular hypertrophy, pericardial effusion.

Normal

Pericardial effusion.



Inferior Vena Cava entering right atrium.



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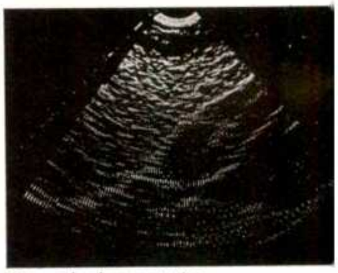
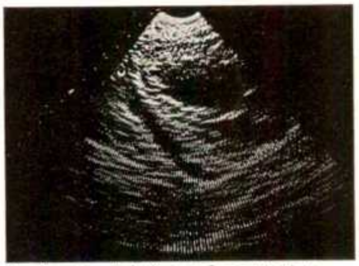


Tricuspid valve vegetation.



Small pericardial effusion, long axis view.

Pericardial effusion, short axis view.

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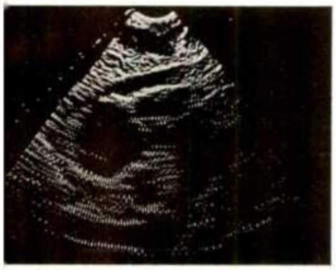
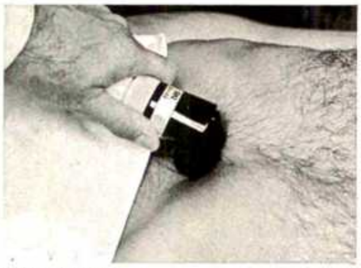
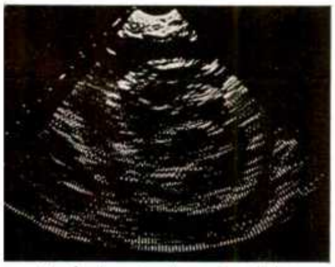


cardial effusion.



Subxyphoid Views



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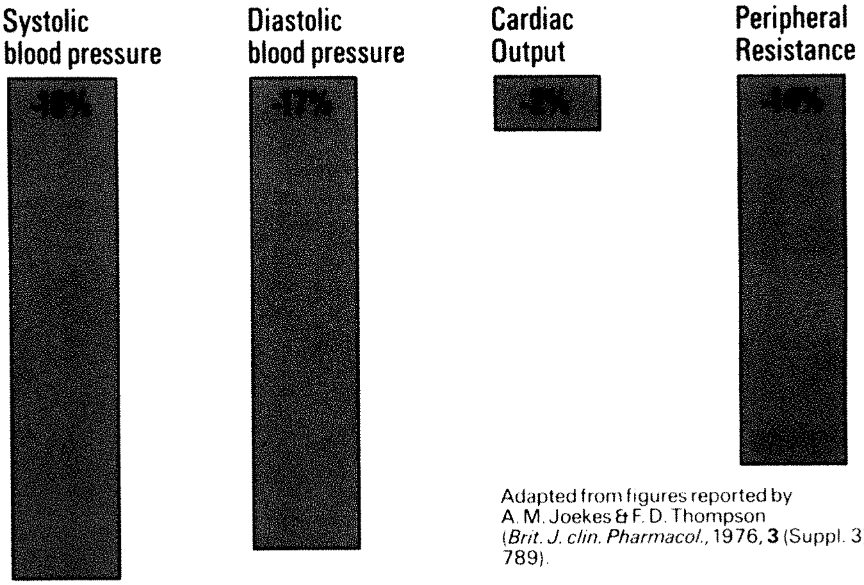

Adapted from figures reported by A. M. Joekes & F. D. Thompson (*Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 789).

The above figure shows the mean haemodynamic changes in 14 hypertensive patients given intravenous Trandate 0.5-1.0mg/kg

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R AS A CONTINUOUS INFUSION...

Labetalol, given slowly by graded intravenous infusion, with continuous onitoring of arterial pressure, is our current treatment of choice in ypertensive emergencies." (Brown, J. J. et al, *Lancet*, 1977, **i**, 1147)

ubsequent treatment can be continued with the same drug
iven orally

A practical advantage associated with labetalol is that oral treatment an be instituted immediately after using the intravenous form."
(Rønne-Rasmussen, J. O. et al, *Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 805)

There are many advantages to using a compound that can be given ntravenously to control blood pressure in patients with small vessel isease or impaired renal function, which is then available for long-term ral therapy."
(Joekes, A. M. & Thompson, F. D., *Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 789–793)

randate Tablets provide effective therapy in all grades
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n this study (oral) labetalol reduced the blood pressure significantly in group of patients with severe, drug-resistant hypertension."
(Morgan, T. et al, *Med. J. Australia*, 1978, **i**, 393)

Complete control of the blood pressure could hardly be expected in this roup of patients and it was rewarding to obtain a very useful reduction both the systolic and diastolic pressures in such a high percentage ith a simple treatment regimen (oral Trandate)."
(Altman, M., *J. Pharmacotherapy*, 1978, **1**, 208)

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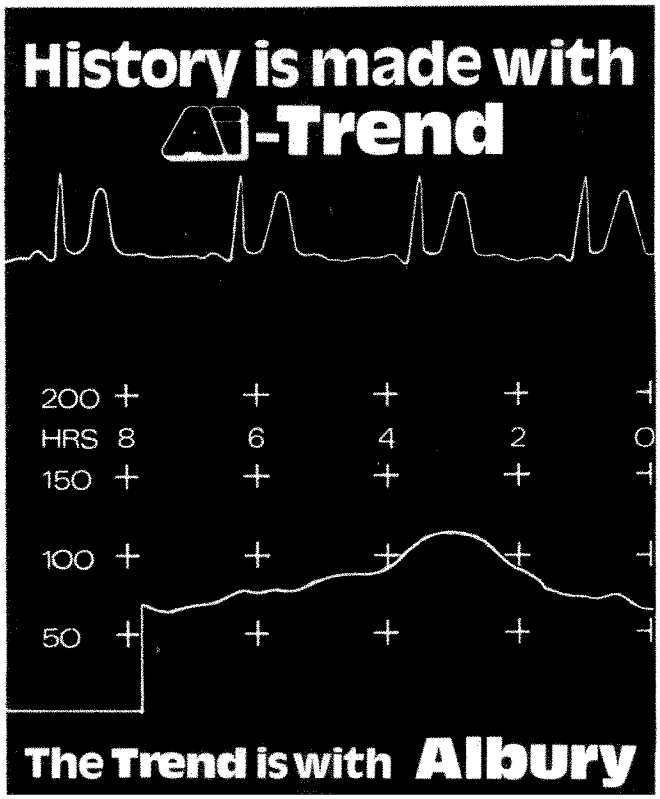

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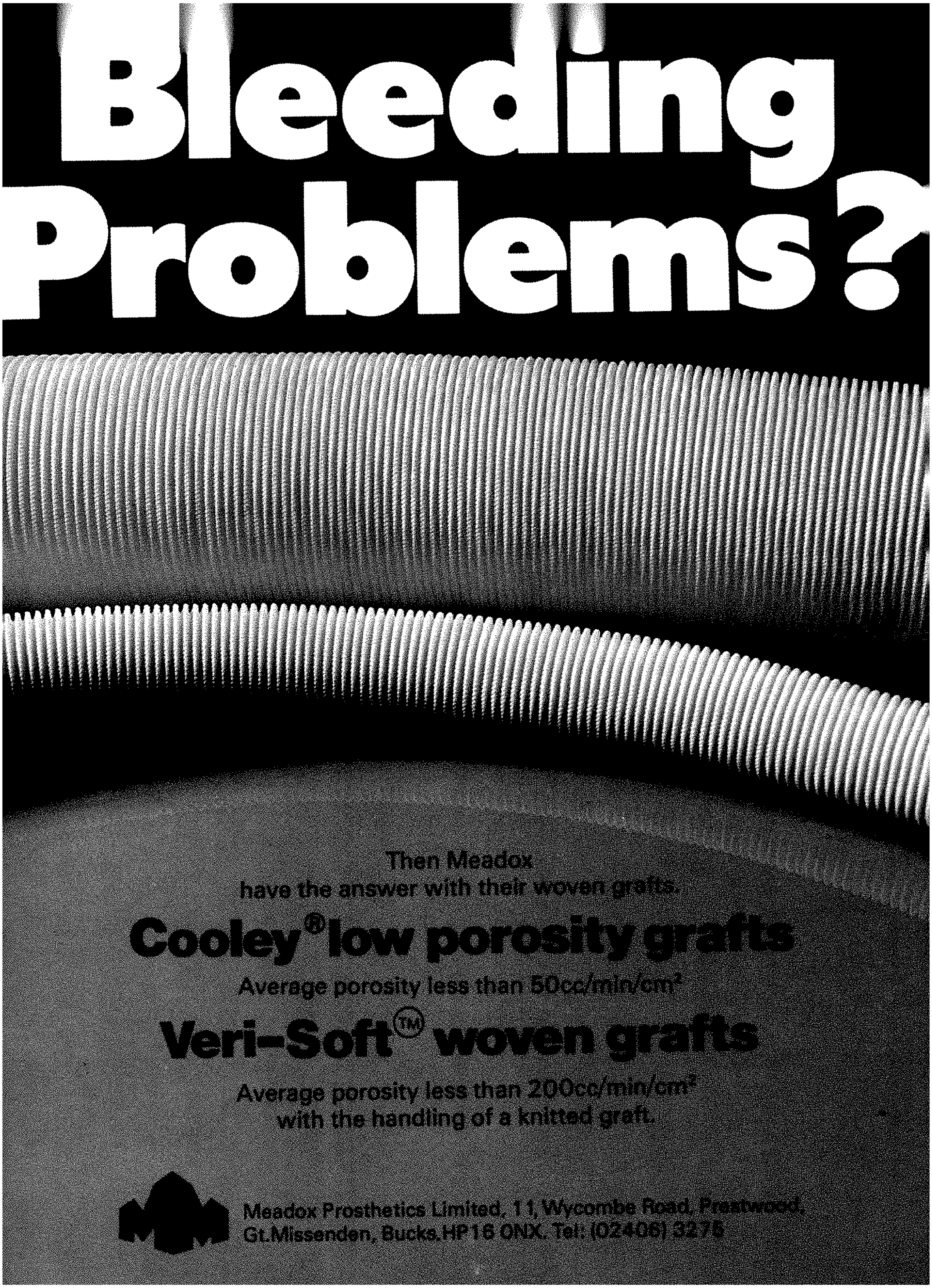

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British Heart Journal, 1979, **42**, 621–632

Morphology and classification of atrioventricular defects

GIAN PIERO PICCOLI[1], LEON M. GERLIS, JAMES L. WILKINSON, KAROLYI LOZSADI, FERGUS J. MACARTNEY[2], AND ROBERT H. ANDERSON[2]

From the Department of Paediatrics, Cardiothoracic Institute, Brompton Hospital, London; Department of Pathology, Grimsby General Hospital, South Humberside; Institute of Child Health, Alder Hey Children's Hospital, Liverpool; Department of Paediatric Surgery, Semmelweis Medical University, Budapest, Hungary; and Thoracic Unit, The Hospital for Sick Children, London

SUMMARY Anatomical studies were made on 114 necropsy specimens of atrioventricular defects with atrioventricular concordance. The malformation is characterised by disproportion between the ventricular inlet and outlet dimensions and a malorientation of the aortic valve relative to the atrioventricular valve or valves. Associated with this there is a characteristic 'scooped-out' appearance of the muscular ventricular septum, gross abnormalities of the membranous components of the septum as compared with the normal heart, and narrowing of the aortic outflow tract. Hearts with these anatomical features can be divided into partial and complete forms depending on the morphology of the atrioventricular annuli. In the partial form the septal leaflets are conjoined to give separate mitral and tricuspid orifices, the conjoined leaflets being displaced into the ventricles and usually attached to the crest of the septum. In the complete form, anterior and posterior components of the 'septal' leaflets are separate, so that a single valve orifice connects the atrial to the ventricular chambers. Further subdivision of the complete form, apart from the morphology of the anterior leaflet, is dependent upon the presence or absence of an ostium primum atrial septal defect.

Many papers have been published on the varying morphology of atrioventricular defects ('atrioventricular canal malformations') (Rogers and Edwards, 1948; Wakai and Edwards, 1956, 1958; Van Mierop *et al.*, 1962; Frater, 1965; Rastelli *et al.*, 1966; Van Mierop and Alley 1966; Rastelli *et al.*, 1967; Goor *et al.*, 1968; Rastelli *et al.*, 1968; Bharati and Lev, 1973; Tenckhoff and Stamm, 1973; Goor and Lillehei, 1975; Ugarte *et al.*, 1976; Van Mierop, 1977).

It is evident from those investigations that opinion is by no means unanimous concerning several important features of these anomalies. For example, there is disagreement concerning the meaning of the so-called intermediate (Wakai and Edwards, 1958) or transitional type (Wakai and Edwards, 1956; Al Omeri *et al.*, 1965; Sumner *et al.*, 1967; Goor and Lillehei, 1975) of atrioventricular defects.

There is disagreement as to whether a cleft between anterior and posterior components of the mitral valve (Van Mierop and Alley, 1966) or an ostium primum atrial septal defect (Goor and Lillehei, 1975) are necessary for definition of an atrioventricular defect. It may be asked whether atrioventricular defects are characterised only by shortness of the inflow portion of the left ventricle (Goor *et al.*, 1968; Tenckhoff and Stamm, 1973; Ugarte *et al.*, 1976) or if there is also lengthening of the left ventricular outflow tract (Van Mierop *et al.*, 1962; Gerbode *et al.*, 1967). Finally, it may be asked what are the anatomical features that are the essence of atrioventricular defects.

We have tried to solve some of these problems by anatomical analysis of specimens catalogued as exhibiting an atrioventricular defect or one of its varieties.

Subjects and methods

We studied specimens from the pathological collections of the Brompton Hospital, London; The Hospital for Sick Children, London; the Royal Liverpool Children's Hospital, Liverpool; Grimsby General Hospital, South Humberside; and the Department of Paediatric Pathology, University of Sheffield, Sheffield.

In all the specimens, we analysed the following:

---

[1] G. P. P. was a visiting fellow from Ospedale GM Lancisi, Ancona, Italy.

[2] F. J. M. and R. H. A. are supported by the British Heart Foundation together with the Vandervell Foundation and the Joseph Levy Foundation, respectively.

Received for publication 20 December 1978

(a) the atrioventricular fibrous annulus; (b) the relation of the inlet and outlet tracts of the left ventricle to each other, as described by Goor *et al.* (1968), and in relation to the distance between the lowest portion of the interventricular septum and the apex of the left ventricle; (c) the constituents of the interventricular muscular septum; (d) the left ventricular outflow tract; (e) in the presence of an anterior common leaflet, the type of attachment of its right and left ventricular components; (f) in the absence of an anterior common leaflet, the type of attachment of the anterior component of the mitral valve; and (g) the degree of fusion between the septum primum and the plane of the atrioventricular valve.

We examined only specimens with a concordant atrioventricular connection and we excluded cases with discordant ventriculoarterial connections or single outlet of the heart. In all, 114 cases were included in our study group.

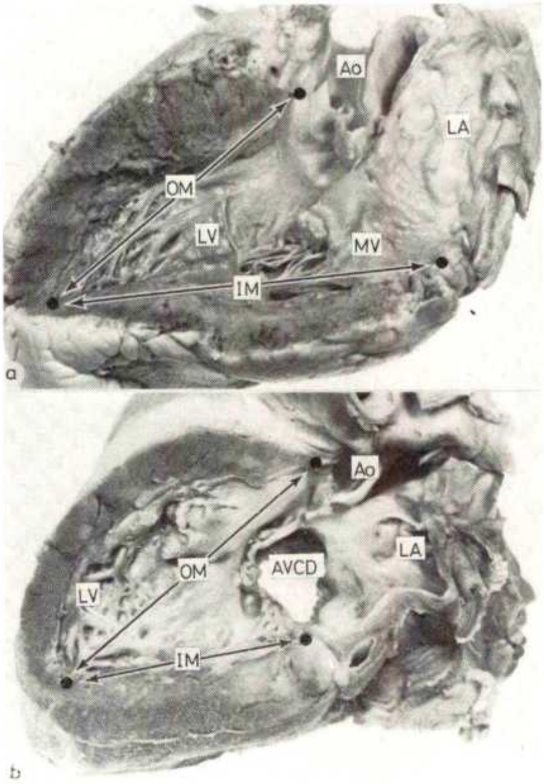

Fig. 1 *Photographs of longitudinal sections of the normal left ventricle (Fig. 1a) and the left ventricle in an atrioventricular defect (Fig. 1b). The photographs show the inlet (IM) and outlet (OM) measurements taken. Note that in the atrioventricular defect there is disproportion between these measurements. (LA, left atrium; LV, left ventricle; MV, mitral valve; Ao, aorta; AVCD, atrioventricular canal defect).*

Results

In all the hearts studied, it was found that firstly the inferior edge of the atrial septum was abnormal in its attachment to the atrioventricular annulus fibrosus. Secondly, the membranous component of the cardiac septum was abnormally positioned and formed. Thirdly, the plane of the atrioventricular orifices was abnormal. Fourthly, the inlet portion of the ventricular septum was deficient (scooped-

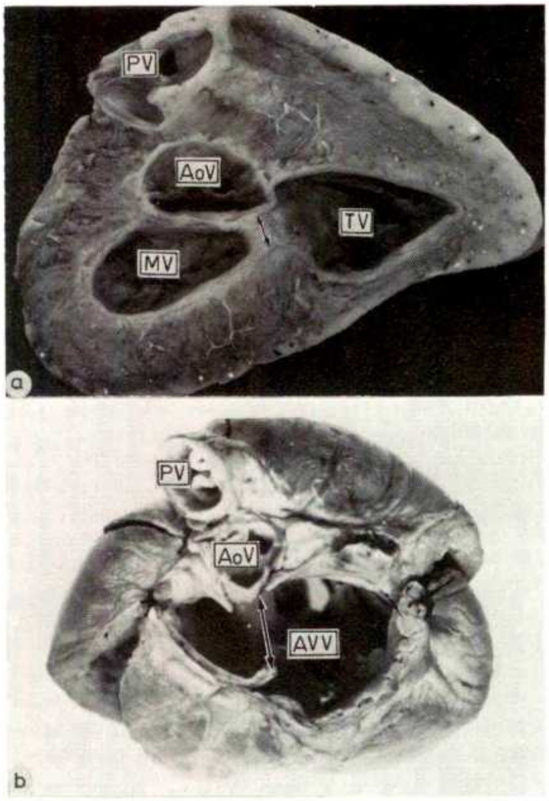

Fig. 2 *Photographs of the atrioventricular junctions of a normal heart (Fig. 2a) and a heart with an atrioventricular defect (Fig. 2b). The hearts are viewed from above. Note that in Fig. 2a the aortic valve (AoV) is wedged between the mitral and tricuspid valves (MV, TV). There is only a short distance at the septal contiguities* (arrowed). *In contrast, in atrioventricular defects (Fig. 2b) the aortic valve does not occupy a wedge position and the atrioventricular orifice is 'sprung'. In the specimen illustrated there is a common atrioventricular valve (AVV). (PV, pulmonary valve.)*

out) in its central portion, and, finally, the aortic valve was abnormally positioned and orientated (Fig. 1, 2). There was considerable variation in the degree of formation of the septal structures and the atrioventricular valves within this pattern of disordered morphology (Table). The hearts could basically be divided into two groups: those with two discrete atrioventricular annuli and those with a common annulus.

Table *Atrioventricular defects*

Two divided atrioventricular annuli: partial forms
- (a) Isolated cleft between anterior and posterior component of mitral valve with abnormally attached mitral valve: one case
- (b) Isolated inlet ventricular septal defect with cleft between anterior and posterior component of mitral valve: one case
- (c) Ostium primum atrial septal defect with abnormally attached but not clefted mitral valve: two cases
- (d) Ostium primum atrial septal defect with cleft between anterior and posterior component of the mitral valve: 32 cases
    - with complete cleft: 26 cases
    - with incomplete cleft: six cases
    - with double cleft: three cases
    - with partial cleft of tricuspid valve: 11 cases
- (e) Ostium primum atrial septal defect with inlet ventricular septal defect but with two separate atrioventricular valves: eight cases
    - (i) with isolated cleft between anterior and posterior component of the mitral valve: three cases
    - (ii) with cleft between anterior and posterior component of mitral valve associated with cleft of septal leaflet of tricuspid valve: three cases
    - (iii) with isolated cleft of septal leaflet of the tricuspid valve: two cases

Common atrioventricular fibrous annulus: complete forms
- (a) Ostium primum atrial septal defect confluent with inlet ventricular septal defect: 66 cases
    - without anterior bridging leaflet: six cases
    - with an anterior bridging leaflet: 60 cases

HEARTS WITH TWO VALVE ANNULI

We found separate fibrous annuli of the atrioventricular valves in 44 cases. One of these hearts exhibited only an isolated cleft between the anterior and posterior component of the mitral valve. Though the atrial and ventricular septa were intact, the two components of the mitral valve were abnormally attached to the interventricular septum, along a line concave towards the atria. The atrial septal attachment was therefore similarly abnormal. The interventricular muscular septum showed the classical 'scooped-out' appearance (Fig. 3).

In one heart, a cleft between the anterior and posterior component of the mitral valve was present, without an ostium primum atrial septal defect, but with a scalloped-out appearance of the interventricular septum and a perimembranous ventricular septal defect.

In two hearts ostium primum atrial septal defects were present without any cleft between the anterior and posterior components of the mitral valve (Fig. 4). There was a lowering of the medial insertion of the mitral fibrous annulus on the superior edge of the interventricular muscular septum, which was deficient in its central portion.

In 32 hearts ostium primum atrial septal defects were present together with cleft mitral valves and the scooped-out appearance of the interventricular septum. The septal annulus separating the mitral and tricuspid septal leaflets was displaced into the ventricles and firmly attached to the crest of the septum (Fig. 5a). In 26 of the 32 cases (81%) the cleft of the mitral valve was complete, that is it extended to the septal annulus. In the remaining hearts the cleft was incomplete. In three of these

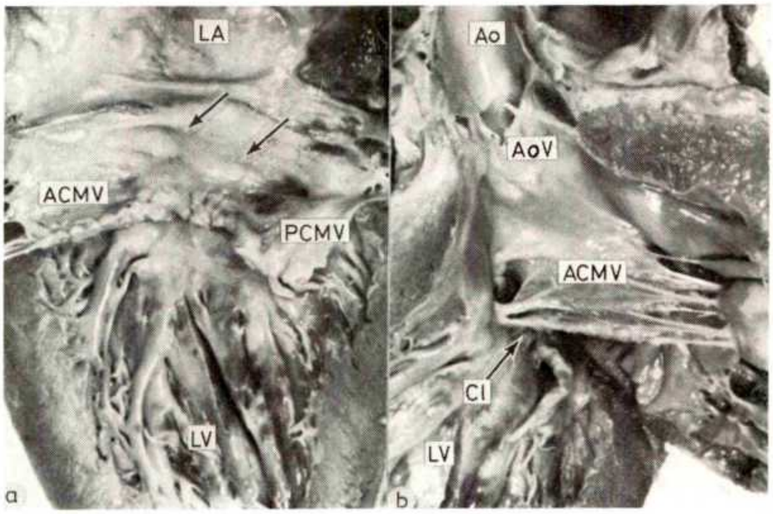

Fig. 3 *Photographs showing a specimen with an isolated cleft of the mitral valve. Fig. 3a shows the left atrium (LA) leading to the left ventricle (LV). The atrial septum is intact* (arrows). *Note the cleft between the anterior and posterior components of the anterior leaflets of the mitral valve (ACMV, PCMV). Fig. 3b shows the left ventricular outflow tract. The cleft (Cl) is seen and the anterior component is attached to the elongated outlet septum. Other abbreviations as before.*

hearts a double cleft was present. In 11 of these hearts, the septal leaflet of the tricuspid valve was divided into discrete anterior and posterior components, the dividing notch extending to the conjoined septal annuli (Fig. 6).

In eight hearts ostium primum atrial septal defects were associated with inlet perimembranous ventricular septal defects. Of these eight hearts, three exhibited a cleft of the mitral valve alone; three had an incomplete cleft of the mitral valve together with discrete anterior and posterior components of the septal leaflet of the tricuspid valve; two did not have mitral clefts (Fig. 7), but one of these exhibited discrete components of the septal leaflet of the tricuspid valve.

HEARTS WITH COMMON ATRIOVENTRICULAR ORIFICE

Seventy cases were found with a common atrioventricular fibrous annulus (Fig. 5b, c).

In 66 of the hearts an ostium primum atrial septal defect was confluent with an inlet ventricular septal defect.

In the remaining four hearts, the edge of the atrial septum extended down to the level of the atrioventricular annulus. Thus, in these hearts, the ostium primum defect was lacking, though there was a common atrioventricular annulus (Fig. 8).

Among the cases with common annulus, six lacked a bridging anterior leaflet. In these hearts, the anterior part of the canal was guarded by two leaflets, one totally committed to the left ventricle and the other totally committed to the right ventricle. The two leaflets were each attached to the crest of the septum, the space between them being the septal crest. In the remaining 64 cases, there was a bridging anterior leaflet. In 39 of these cases the right lateral edge of the bridging anterior leaflet was attached to the superior edge of the muscular septum and, extending across the septum, to the medial papillary muscle.

In eight cases the right lateral insertion was to a 'medial' papillary muscle, displaced from its usual position towards the ventricular apex. In the remaining 17 cases the lateral attachment was to the anterolateral papillary muscle of the right ventricle. The interventricular septum showed always a 'scooped-out' appearance.

COMMON FEATURES

Measurement of the lengths of the inlet septum compared to the outlet septum (Fig. 9) showed that the outlet tract of the left ventricle was always lengthened in relation to its inlet portion. The diaphragmatic length of the inlet septum was greater than the central portion, which constituted the shortest length of the ventricular septum (Fig. 10, 11). In general, the degree of lengthening was greater in the hearts with a common annulus than in those with separate mitral and tricuspid annuli.

In all the hearts the aortic valve was deviated anteriorly, when compared with the normal hearts, and in 90 cases it was deviated rightward (Fig. 12).

The outflow tract was narrowed as judged from anatomical observation in 68 hearts (Fig. 13).

This tract was larger than normal only in the three cases with complete defects associated with tetralogy of Fallot. (In these hearts the perimem-

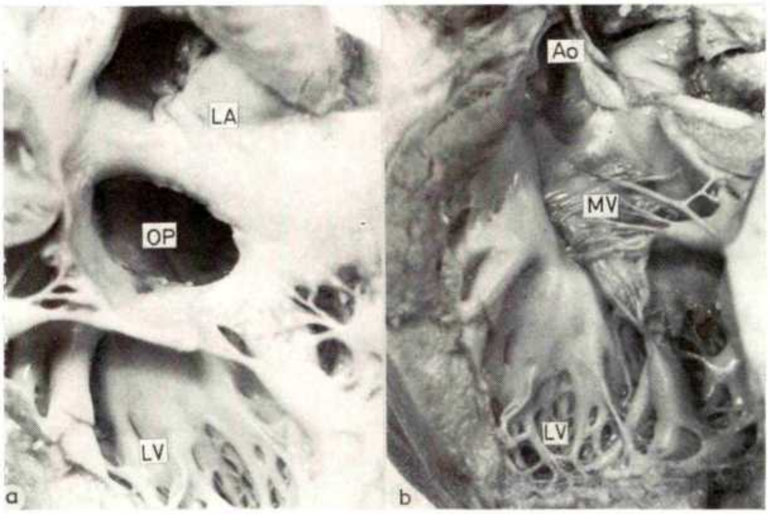

Fig. 4 *Photographs illustrating the morphology of an atrioventricular defect with an ostium primum atrial septal defect (OP). Fig. 4a shows the defect viewed from the left. There is no cleft in the mitral valve. Fig. 4b shows the typical atrioventricular defect outflow tract. Abbreviations as before.*

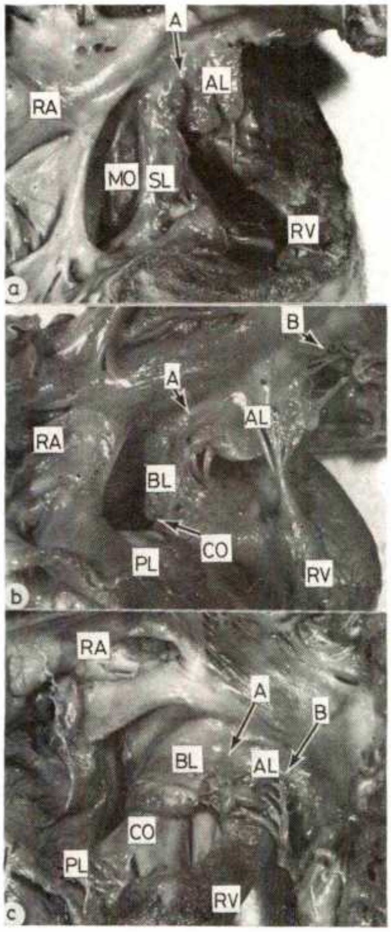

Fig. 5 *Photographs illustrating the morphology of ostium primum atrioventricular defect with a cleft mitral valve (Fig. 5a) and complete atrioventricular defects (Fig. 5b, c). In Fig. 5a the opened tricuspid orifice is seen. The discrete mitral orifice (MO) is viewed through the ostium primum defect. The septal leaflets of mitral and tricuspid valves are fused both to each other and to the ventricular septum (SL). The narrow septal commissure of the tricuspid valve is seen (A) and is to the right of the atrial septal insertion to the annulus. It separates the septal leaflet of the tricuspid valve from the anterior leaflet (AL). Fig. 5b shows the comparable anatomy of a complete atrioventricular defect. However, there is now a common orifice (CO) caused by the separation of the anterior and posterior components of the septal leaflets of the atrioventricular valves. The antero-superior commissure (A) now separates the anterior bridging leaflet (BL) from the anterior leaflet of the tricuspid component. This in turn is separated from the lateral leaflet by commissure B. Note also the posterior bridging leaflet (PL). Fig. 5c shows a common atrioventricular defect with a greater degree of bridging of the left anterior leaflet.*

branous defect extended into the infundibular region because of anterior deviation of the infundibular septum. A confluent perimembranous defect therefore extended from the crux to the insertion of the infundibular septum.)

In the hearts with two annuli, in the absence of an inlet defect, an interventricular component of a membranous septum was present beneath the attachment line of the anterior component of the mitral valve to the superior edge of the interventricular muscular septum.

In the cases with inlet ventricular septal defect, the interventricular communication was bounded at the level of the infundibular septum by a remnant of the interventricular membranous septum in all the hearts with two annuli and in 48 cases (68%) with common annulus (Fig. 14a).

A fibrous structure between the left ventricle and the right atrium was always present and was comparable with the outlet component of the atrioventricular membranous septum (Fig. 14b).

Discussion

The hallmarks of an atrioventricular defect are, firstly, a disproproportion between the inlet and outlet length of the ventricular septum and, secondly, a malorientation of the aortic valve relative to the atrioventricular valve or valves (Van Mierop *et al.*, 1962; Van Mierop and Alley, 1966; Goor and Lillehei, 1975; Van Mierop, 1977). Atrial or ventricular septal defects and malformations of the atrioventricular valves can accompany these basic anatomical features, and the combination of these anomalies produces the variation seen in the malformation (Fig. 15).

By atrioventricular defects, therefore, we describe a continuous spectrum of malformations characterised by: (1) 'scooped-out' appearance of the interventricular septum (Campbell and Missen, 1957; Van Mierop *et al.*, 1962; Somerville, 1966; Van Mierop and Alley, 1966; Gerbode *et al.*, 1967; Goor *et al.*, 1968; Tenckhoff and Stamm, 1973; Goor and Lillehei, 1975; Ugarte *et al.*, 1976; Van Mierop, 1977; Ebert and Goor, 1978); (2) abnormal attachment of the atrioventricular leaflets to the rim of the interventricular septum (Van Mierop *et al.*, 1962; Van Mierop and Alley, 1966; Van Mierop, 1977); (3) abnormal attachment of the inferior edge of the septum primum to the atrioventricular plane (Rogers and Edwards, 1948; Wakai and Edwards, 1956, 1958; Van Mierop *et al.*, 1962; Van Mierop and Alley, 1966; Goor and Lillehei, 1975; Van Mierop, 1977); (4) lengthening and narrowing of the left ventricular outflow tract (Van Mierop *et al.*, 1962; Van Mierop and Alley,

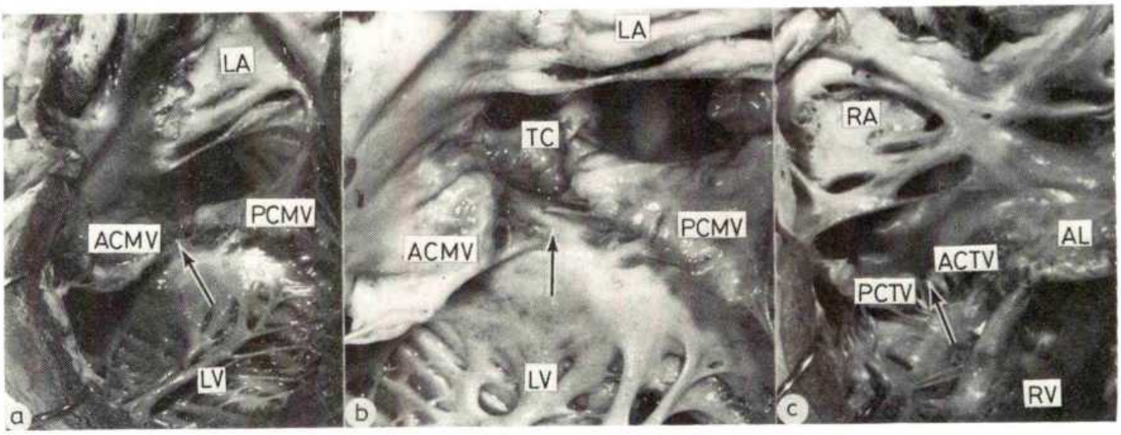

Fig. 6 *Photographs illustrating a specimen with clefts between the anterior and posterior components of both mitral and tricuspid valves (ACMV, PCMV, ACTV, PCTV) but despite this separation still with discrete mitral and tricuspid orifices. Fig. 6a and 6b are viewed from the left and Fig. 6c from the right. The arrows point to the clefts. Other abbreviations as before.*

1966; Gerbode *et al.,* 1967; Van Mierop, 1977) together with a rightward and anterior deviation of the aorta (Van Mierop *et al.,* 1962; Van Mierop and Alley, 1966; Van Mierop, 1977); and (5) abnormal conformation of the membranous septum.

Our results show that the different anomalies can be divided into two basic constellations; namely, those with separate mitral and tricuspid annuli (partial atrioventricular defects) and those with a common atrioventricular annulus (complete defects). Our observations suggest that from the anatomical viewpoint, the group of anomalies termed transitional or intermediate types (Wakai and Edwards, 1956, 1958; Al Omeri *et al.,* 1965; Sumner *et al.,* 1967) are best considered as variants of the partial form in that they have discrete mitral and tricuspid annuli. It is true that the discrete annuli are in many instances produced as a consequence of a bridge of valve tissue extending across the septum from posterior to anterior leaflets and that the conjoined valves have features that resemble a common orifice (Fig. 6). It is also true that from the surgical standpoint these anomalies have features

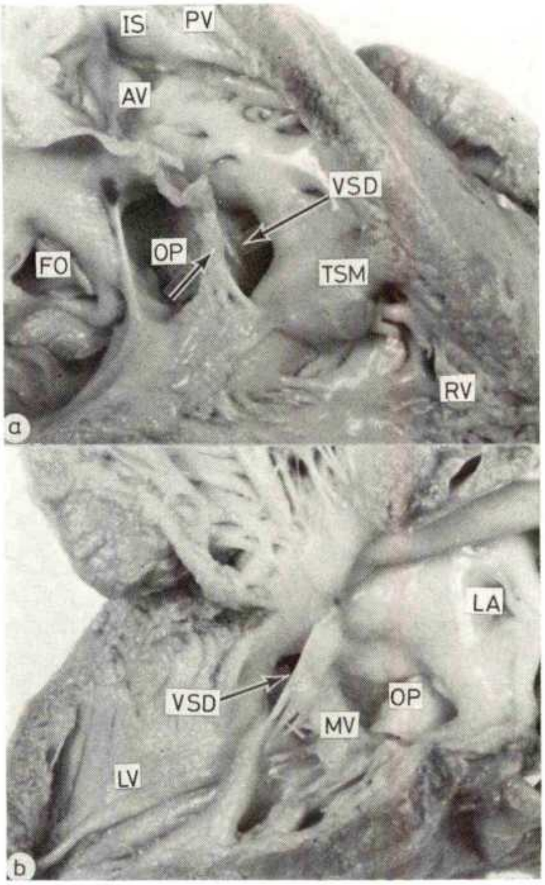

Fig. 7 *Photographs illustrating the morphology of an atrioventricular defect with an ostium primum atrial septal defect, a perimembranous inlet ventricular septal defect (VSD) but discrete mitral and tricuspid orifices without a cleft* (arrows). *Fig. 7a is viewed from the right ventricle and shows double outlet from this ventricle; the aorta (AV) and pulmonary artery (PV) being separated by the infundibular septum (IS). (FO, fossa ovalis; TSM, trabecular septomarginalis.) Fig. 7b shows the left ventricular aspect.*

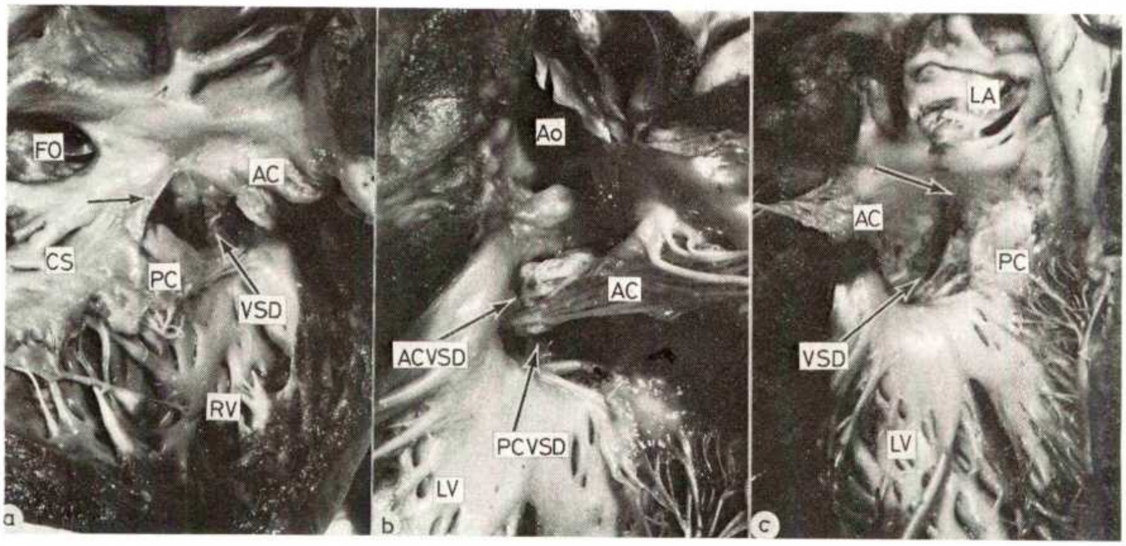

Fig. 8 *Photographs illustrating the morphology of a complete atrioventricular defect without an ostium primum atrial septal defect. Fig. 8a shows the right aspect of the malformation. Both anterior and posterior leaflets (AC, PC) bridge through the ventricular septal defect to the left ventricle. Fig. 8b and 8c show the left ventricular aspect, viewed from the outflow tract (Fig. 8b) and the inlet aspect (Fig. 8c). The anterior component of the common AV valve (AC) separates the ventricular septal defect into anterior (ACVSD) and posterior (PCVSD) components. Note that the atrial septum is intact* (arrowed) *and extends down to the level of the atrioventricular annulus. (CS, coronary sinus; other abbreviations as before.)*

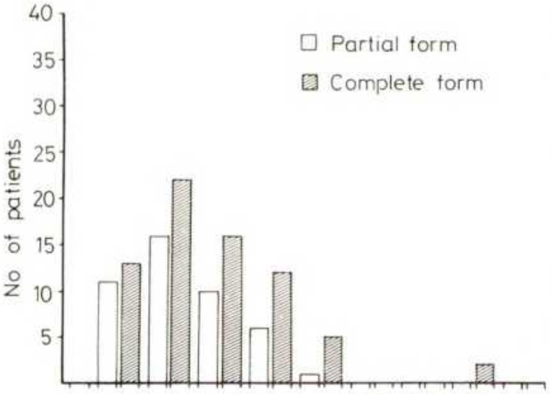

Fig. 9 *Ratio between the lengths of the outlet septum and the diaphragmatic portion of the inlet septum. The length of the outlet septum was always greater than that of the diaphragmatic portion of the inlet septum. This disproportion was more evident in the complete than in the partial types of atrioventricular defects. This ratio in the normal hearts is 1.*

more in common with the complete form of the malformation particularly when a large ventricular defect is present beneath the bridging leaflet tissue. None the less, to our minds the presence of bridging leaflet tissue produced two discrete annuli and permits their unequivocal categorisation on anatomical grounds as partial malformations. Indeed, we observed one heart in which an ostium primum atrial septal defect was associated with a ventricular septal defect and partitioned mitral and tricuspid annuli, in the absence of any clefts in their septal components (Fig. 7). These considerations highlight the problems engendered by usage of the adjectives 'partial' and 'complete' as applied to atrioventricular defects. We, believing we were conforming to common usage, used the terms to differentiate cases with partitioned tricuspid and mitral orifices from those with a common orifice. But it has been pointed out to us that an alternative approach (Brandt *et al.*, 1972) is to use the term 'partial' to describe cases without a ventricular septal defect, 'complete' to describe those with a ventricular septal defect, and to use 'intermediate' in yet another way, namely to describe cases with a small ventricular septal defect (J. B. Partridge, 1979, personal communication). Thus the problems engendered by the 'intermediate' category relate to

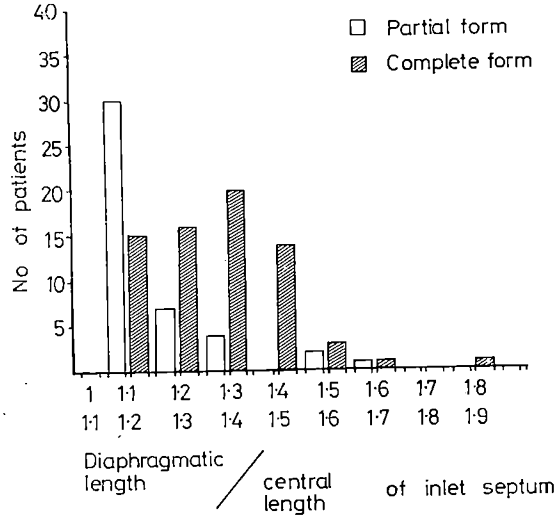

Fig. 10 *Ratios between the lengths of the diaphragmatic and central portion of the inlet ventricular septum. The diaphragmatic length of the inlet septum was always greater than the central portion. This disproportion was more evident in the complete than in the partial types of atrioventricular malformations. This ratio in the normal hearts is 1.*

the use of the terms 'partial' and 'complete'. In that we are using these adjectives to describe annular morphology, they are not ideal. It would be far more appropriate to divide our cases into groups with *partitioned* orifices (presently termed 'partial defects') and those with a *common* orifice (presently termed 'complete defects'). We have continued to use the terms 'partial' and 'complete' in this and our other papers (Macartney *et al.,* 1979; Piccoli *et al.,* 1979) in deference to what we believe is common usage, but we suggest that in future it will be better to differentiate atrioventricular defects on the basis of their annular morphology into cases with partitioned mitral and tricuspid orifices and cases with a common atrioventricular orifice.

There has been considerable discussion regarding the substrate of the disproportion of the inlet and outlet length of the ventricular septum. Many authors have indicated that there is a shortening of the diaphragmatic wall of the left ventricle (Goor *et al.,* 1968; Tenckhoff and Stamm, 1973; Blieden *et al.,* 1974; Ugarte *et al.,* 1976). Yet others have indicated that the infundibular septum is excessively long (Van Mierop *et al.,* 1962; Van Mierop and Alley, 1966; Gerbode *et al.,* 1967). Our findings indicate that all of these factors are present (Fig. 9, 10, 11). Measurement of the inlet septum and comparison with the length of the outlet septum do not permit deductions concerning the shortness of one or the excessive length of the other. It is more likely that a combination of these factors exists.

There has also been disagreement regarding which part of the membranous septum is missing in atrioventricular canal malformations. Some have suggested that all the membranous portion of the ventricular septum is lacking (Rogers and Edwards, 1948; Wakai and Edwards, 1956; Campbell and Missen, 1957; Wakai and Edwards, 1958; Neufeld *et al.,* 1961). Others have suggested that the atrioventricular membranous septum together with the basal portion of the muscular ventricular septum are missing (Van Mierop *et al.,* 1962; Al Omeri *et al.* 1965; Somerville, 1966; Van Mierop and Alley, 1966; Somerville and Jefferson, 1968). Yet others pointed to a deficiency in the muscular rim beneath the membranous septum which extended to the diaphragmatic wall of the left ventricle (Goor *et al.,* 1968) or to the subaortic area (Blieden *et al.,* 1974). Our observations substantiate the view that the crest of the inlet septum is deficient in the perimembranous area. However, we would not agree that the membranous septum is always absent.

Discussion regarding this point devolves upon definitions of the membranous septum. In all the hearts studied, the septal edge of the anterior components of the atrioventricular valves is inter-

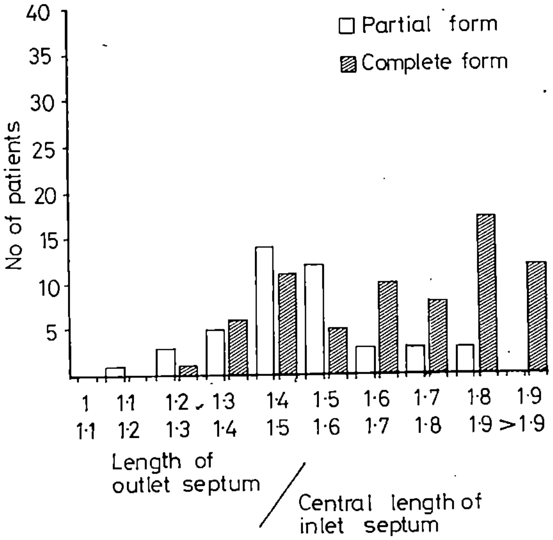

Fig. 11 *Ratio between the lengths of the outlet septum and the central portion of the inlet septum. The length of the outlet septum was always greater than that of the central portion of the inlet septum. This disproportion was more evident in the complete than in the partial types of atrioventricular defects. This ratio in the normal hearts is 1.*

posed between the left ventricular outflow tract and the right atrium. Therefore, it constitutes an atrioventricular component of a membranous septum (Fig. 8b). It occupies a different position from that found in the normal heart, being deviated anteriorly. In addition, in the malformations without perimembranous ventricular septal defect, the insertion line of the conjoined annuli of the mitral and tricuspid valves on the interventricular septum represents an interventricular membranous septum. In the malformations with perimembranous septal defect, a remnant of the interventricular component of the membranous septum was present in 57 cases (73%). It must be emphasised, however, that a muscular atrioventricular septum was totally lacking in all hearts studied (Brandt *et al.*, 1972), since the tricuspid and mitral annuli were attached to one another at the same level (Van Mierop *et al.*, 1962; Van Mierop and Alley, 1966; Goor *et al.*, 1968). In the normal heart the tricuspid valve is attached to the cardiac septum towards the ventricular apex as compared with the mitral valve. As a consequence of this, a small part of the membranous septum together with part of the inlet muscular septum is placed between the right atrium and the inlet part of the left ventricle. Clearly when, as in atrioventricular defects, the mitral and tricuspid annuli are attached at the same level, these atrioventricular septal components cannot exist.

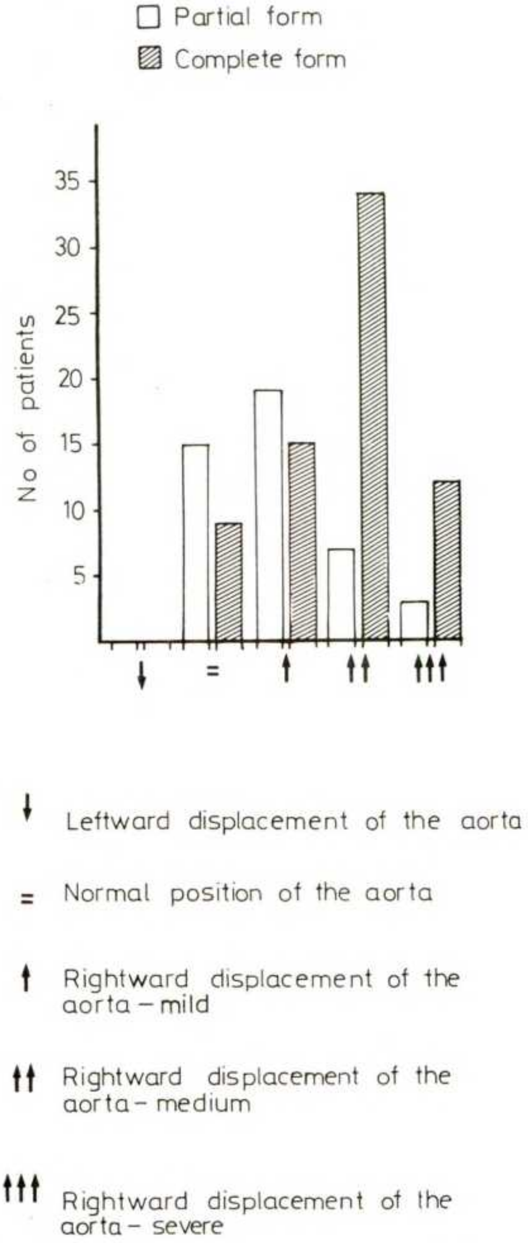

Fig. 12 *Rightward displacement of the aorta. This was a finding characterising 78·1 per cent of the cases. The major degrees of rightward displacement were present in the complete types of atrioventricular defects.*

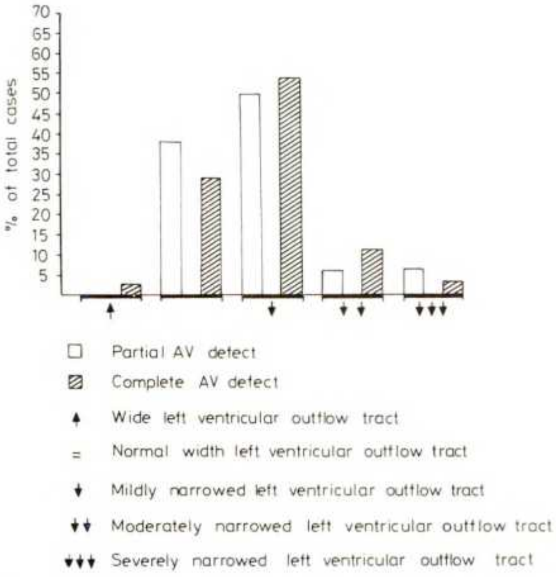

Fig. 13 *Left ventricular outflow tract narrowing. This was found in 68 hearts.*

We observed in our series of partial defects, two hearts in which an ostium primum defect was present without a cleft in the mitral valve. None the less, in these hearts the conjoined mitral and

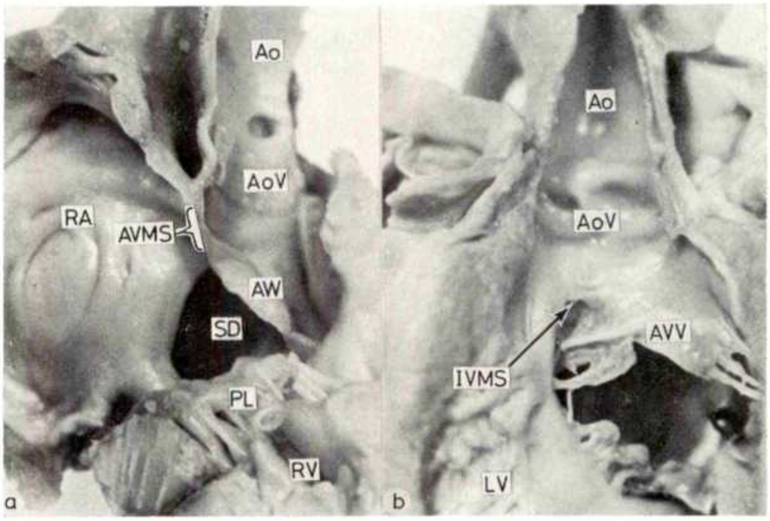

Fig. 14 *Photographs of atrioventricular defects illustrating in Fig. 14a the atrioventricular membranous septum (AVMS) and in Fig. 14b an interventricular membranous septum (IVMS). Fig. 14a has been prepared by sectioning the heart from the right atrium into the aortic outflow tract. (SD, septal defect; other abbreviations as before.) Fig. 14b is viewed from the anterior aspect of the left ventricular outflow.*

tricuspid annuli were attached to the crest of a typical 'scooped-out' ventricular septum, and the hearts had all the features of an atrioventricular defect. This type of malformation has been characterised by Goor *et al.* (1968) as a 'corrected' malformation since haemodynamically it resembles a secondum atrial septal defect.

In the majority of cases of the complete malformation, the atrioventricular orifices were committed in approximately equal portions between the right and left ventricle. In some hearts, however, the orifices were committed primarily to one ventricle with hypoplasia of the other ventricle. This feature was previously noted by Bharati and Lev (1973) and termed right or left ventricular dominance, and a large series of right dominance has recently been identified and described by Freedom *et al.* (1978). Such ventricular dominance was also observed in partial malformations in our series.

Four other cases of the complete malformation were of considerable interest. In these hearts, on first examination it appeared that the atrial septum was intact and that two annuli were formed. On closer evaluation it was seen that the anterior and posterior leaflets were continuous between right and left ventricles, a fibrous rim on the underside of the atrial septum joining together the leaflets. If we compare these cases with the diagram constructed by Goor and Lillehei (1975) for division of the atrial and ventricular components of the complete defect, these cases must be categorised as complete

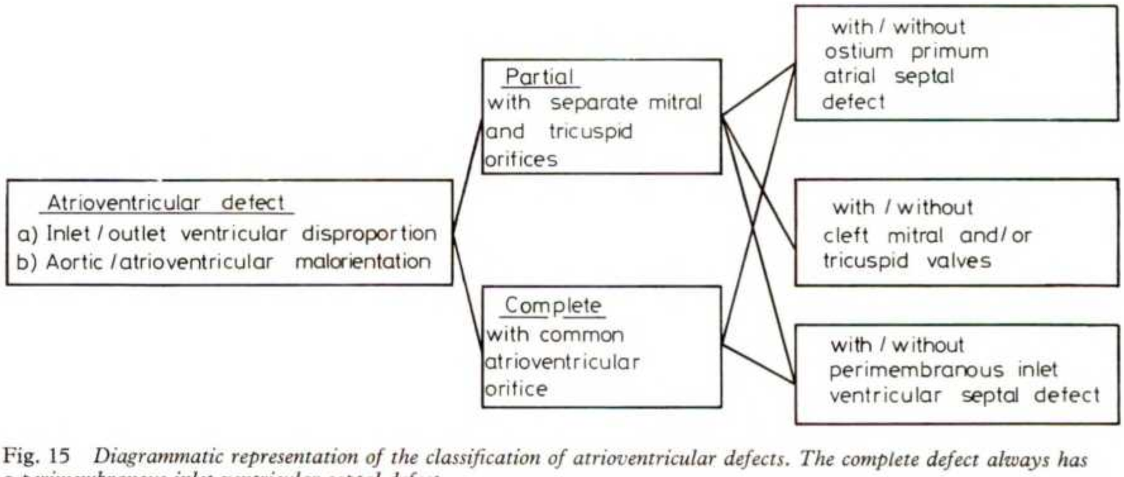
Atrioventricular defect
a) Inlet / outlet ventricular disproportion
b) Aortic / atrioventricular malorientation
Partial
with separate mitral and tricuspid orifices
Complete
with common atrioventricular orifice
with / without ostium primum atrial septal defect
with / without cleft mitral and/ or tricuspid valves
with / without perimembranous inlet ventricular septal defect

Fig. 15 *Diagrammatic representation of the classification of atrioventricular defects. The complete defect always has a perimembranous inlet ventricular septal defect.*

atrioventricular defects without an ostium primum component. An alternative way of expressing this would be to say they were true atrioventricular defects, the interventricular communication being at the atrial aspect of the valve leaflets. They must be distinguished from the so-called 'atrioventricular canal ventricular septal defects' described in partial defects (Neufeld *et al.,* 1961). In many instances, the latter defects are no more than perimembranous defects excavating the inlet portion of the ventricular septum and do not possess the stigmata of the atrioventricular defect itself (see Neufeld *et al.,* 1961, Fig. 8). However, as with so many anomalies, there is a spectrum of malformations depending on the degree of excavation of the inlet septum. In our series of partial canal malformations, we observed a ventricular septal defect in association with a cleft mitral valve but with an intact atrial septum, this case having all the features of an atrioventricular defect. It is our opinion, therefore, that the term 'atrioventricular canal ventricular septal defect', if used at all, should be reserved for description of such cases which have the cardinal features of an atrioventricular defect.

In conclusion, our study indicates that atrioventricular defects are characterised by discrete anatomical features, namely disproportion between ventricular inlet and outlet lengths and abnormal position of the aortic valve. The other cardinal features follow from these primary abnormalities. They can be divided into partial and complete forms, depending upon whether these are separate mitral and tricuspid annuli or a common atrioventricular annulus. However, we believe that, in future, it will be more appropriate to describe these as groups with partitioned orifices or a common orifice rather than with the terms 'partial' and 'complete'. Each of these groups can be further subdivided depending on the presence or absence of an atrial septal defect, a ventricular septal defect, and the variations in morphology of the atrioventricular valve or valves (Fig. 15).

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Morphology and classification of complete atrioventricular defects

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SUMMARY Anatomical studies were made on 70 necropsied hearts with atrioventricular defects from patients with situs solitus and atrioventricular concordance, all having a common atrioventricular orifice. The arterial connections were concordant in 68 and were double outlet right ventricle in two; cases with arterial discordance (transposition) or single outlet of the heart were excluded. It proved possible to subdivide the hearts, depending on the morphology of the valve leaflets. Five leaflets were distinguished by the commissural pattern and their insertion to major papillary muscles. They were a posterior bridging leaflet, right and left lateral leaflets, and right and left anterior leaflets. Subdivision was made on the basis of the disposition of the anterior leaflets. In six hearts the left anterior leaflet was committed to the left ventricle and the right anterior leaflet to the right ventricle, the commissure between them being on the crest of the ventricular septum. In 39 hearts there was minimal bridging of the left anterior leaflet so that it extended between the anterior papillary muscle of the left ventricle and the medial papillary complex of the right ventricle. In eight hearts the right margin of the left anterior leaflet was attached to an apical papillary muscle, while in 17 hearts it was attached to the anterolateral papillary muscle of the right ventricle. As the bridging of the left anterior leaflet increased, so the size of the right anterior leaflet decreased, but in all hearts both leaflets were identified. These findings were compared with previous classifications of complete atrioventricular defects.

The anatomical features of complete atrioventricular defects have been outlined by many authors who pointed out the shortness of the ventricular inlet segments (Rogers and Edwards, 1948; Wakai and Edwards, 1956, 1958; Goor *et al.*, 1968; Blieden *et al.*, 1974) and the excessive length of the outflow tract of the left ventricle (Van Mierop *et al.*, 1962; Van Mierop and Alley, 1966; Gerbode *et al.*, 1967; Van Mierop, 1977). Many investigators have also studied the constitution of the valve leaflets but it is the classification of Rastelli *et al.* (1966, 1967, 1968) based on the arrangements of the anterior leaflets which is most accepted by surgeons.

However, more recent papers have suggested a lack of correspondence between the surgical value of Rastelli's classification and the actual arrangement of the leaflets of the common atrioventricular valve (Tenckhoff and Stamm, 1973; Goor and Lillehei, 1975; Ugarte *et al.*, 1976), while Berger *et al.* (1978) have gone so far as to question its surgical value.

We have analysed 70 specimens of complete atrioventricular defects from an anatomical point of view, excluding any embryological interpretations, and findings relative to these disagreements are presently described.

Subjects and methods

Seventy specimens with complete atrioventricular defects were analysed. They were taken from the pathological collections of the Brompton Hospital, London; The Hospital for Sick Children, London, The Royal Liverpool Children's Hospital; Grimsby General Hospital, South Humberside; and the Department of Paediatric Pathology, University of Sheffield. In all specimens we studied the anatomy of the valve leaflets according to the criteria of Lam *et al.* (1970), Ranganatham *et al.* (1970),

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and Silver *et al.* (1971), the anatomical disposition of the papillary muscles in the right ventricle, and the modality of insertion of the interatrial septum primum at the atrioventricular level.

All the specimens except two were in situs solitus with concordant atrioventricular connection and normal relation of cardiac chambers and great arteries. The two outstanding cases had double outlet right ventricle with the aortic valve in right posterior position.

Results

In all the hearts examined, five leaflets could be identified in the common valve on the basis of the papillary muscle tethering (Fig. 1). They were a posterior bridging leaflet, a left lateral and right lateral (or inferior) leaflet, and two anterior leaflets. The lateral leaflets showed various degrees of 'scalloping' which, in some instances, was sufficiently obvious to suggest the presence of an additional leaflet. However, it was the variation in morphology of the two anterior leaflets which provided the basis for subdivision of the hearts.

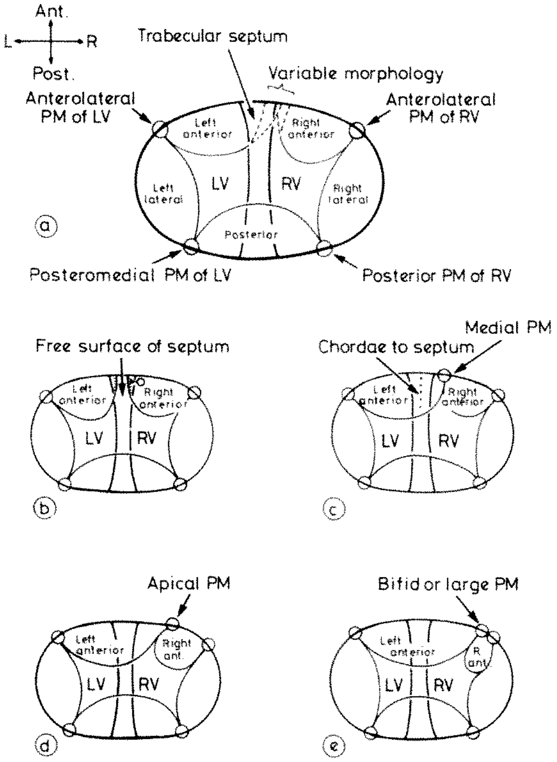

Fig. 1 *Diagram illustrating the variation of the anterior leaflets of complete atrioventricular defects. Fig. 1a shows the position of the leaflets and their supporting papillary muscles. Fig. 1b–1e illustrate the varying morphology of the malformations studied.*

ANTERIOR LEAFLETS COMMITTED TO RIGHT AND LEFT VENTRICLES, RESPECTIVELY (Fig. 1b)

In six cases, the left anterior leaflet extended between the anterolateral papillary muscle of the left ventricle and the crest of the ventricular septum to which it was attached by multiple chordae. The right anterior leaflet extended from the crest of the septum to the anterolateral papillary muscle of the right ventricle, which also supported the right lateral leaflet. The medial papillary muscle complex supported the medial end of the right anterior leaflet, but the crest of the ventricular septum between the leaflet was bare, that is was not bridged by leaflet tissue (Fig. 2).

BRIDGING LEFT ANTERIOR LEAFLET TO MEDIAL PAPILLARY MUSCLE (Fig. 1c)

In 39 cases the left anterior leaflet extended from the anterolateral papillary muscle of the left ventricle to the medial papillary muscle which arose in normal fashion from the posterior limb of the trabecula septomarginalis (Fig. 3). There was variation in the relation of this bridging leaflet to the septal structures. In 33 hearts the leaflet was attached by vertical chords to the trabecular septum as it bridged this septum. In the majority of these hearts, a partially formed interventricular component of the membranous septum joined the bridging leaflet to the infundibular septum, with a portion of the leaflet in the right ventricle (Fig. 3b). The anterior insertion of the atrial septum was in line with the trabecular septum and the interventricular membranous septum, that is to the left of the commissure between the two anterior leaflets (Fig. 3c). There was a discrete commissure between the two anterior leaflets supported by the medial papillary muscle complex. In four additional hearts, the bridging leaflet was not tethered to the trabecular septum but was attached to the infundibular septum via the membranous septal remnant. In the final two hearts, the bridging leaflet was attached only to the medial papillary muscle, having no attachment to the ventricular septum. In all these hearts the right anterior leaflet extended from the medial papillary complex to the anterolateral papillary muscle of the right ventricle. In five of these, an additional bar of muscle extended from the anterolateral muscle mass to the free margin of the leaflet.

BRIDGING LEFT ANTERIOR LEAFLET TO APICAL PAPILLARY MUSCLE (Fig. 1d)

In eight cases, the left anterior leaflet extended from the anterolateral papillary muscle of the left ventricle across the trabecular septum to be attached to a papillary muscle situated on the right ventricular septal surface, towards the ventricular apex (Fig. 4, 5). This muscle supported the commissure between the left anterior and right anterior leaflets, the latter leaflet being smaller in

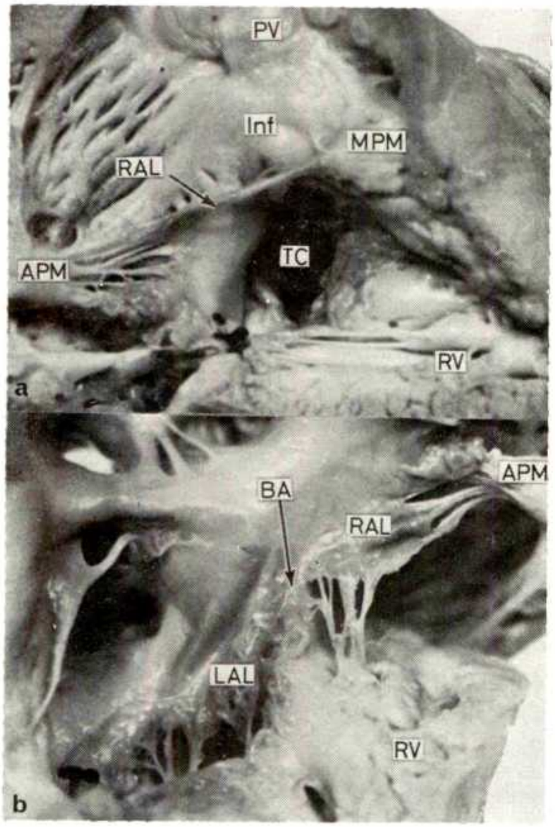

Fig. 2 *An example of an atrioventricular defect of the type shown diagrammatically in Fig. 1b. Fig. 2a shows the view of the right side of the common valve (TC) observed from the infundibular aspect. The right anterior leaflet (RAL) extends from the medial papillary muscle (MPM) to the anterior papillary muscle (APM) of the right ventricle (RV). (Inf, infundibulum; PV, pulmonary valve). Fig. 2b shows a view of the anterior leaflets of the common valve viewed posteriorly from the right atrioventricular junction. The left anterior leaflet (LAL) and the right anterior leaflet are both attached to the septal crest leaving the free surface of the septum bare between their attachments (BA). (Other abbreviations as before.)*

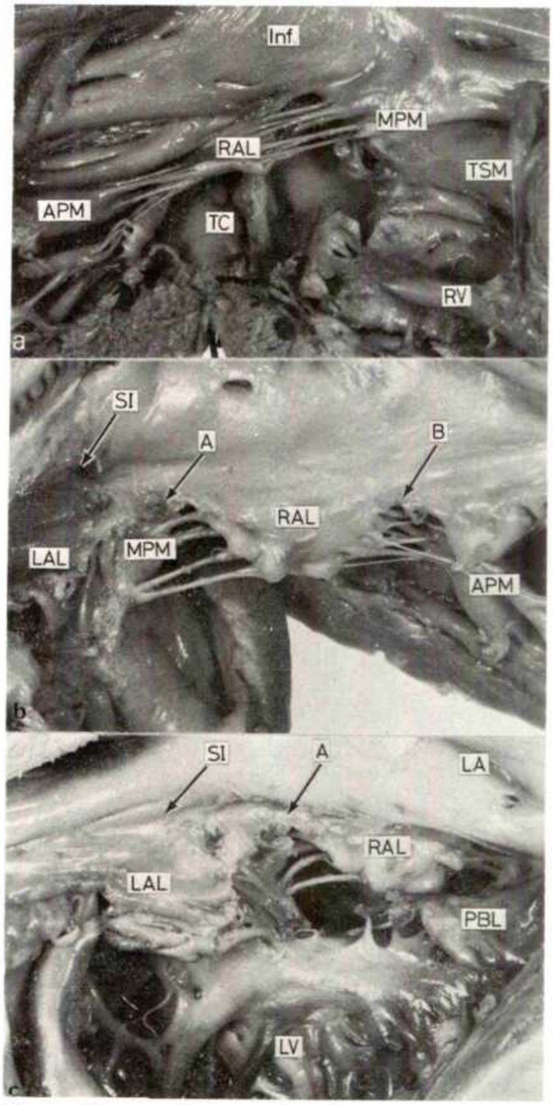

Fig. 3 *Photograph of a specimen illustrating the morphology of the leaflets shown diagrammatically in Fig. 1c. Fig. 3a shows the infundibular view. The right anterior leaflet is again seen extending between anterior and medial papillary muscles. (TSM, trabecular septomarginalis). Fig. 3b shows the leaflets from their right posterior aspect and illustrates how the left anterior leaflet has bridged the septum to be attached by commissural chord A to the medial papillary muscle. The commissure B taking origin from the right anterior papillary muscle is between the right anterior and right lateral leaflets. Note that the insertion of the atrial septum is well to the left of commissure A between the anterior leaflets. Fig. 3c shows the leaflets viewed from their left posterior aspect. (LV, left ventricle; LA, left atrium; PBL, posterior bridging leaflet; other abbreviations as before.)*

size compared with the group in which it was attached to the medial papillary muscle complex. In three of them, the left anterior leaflet was attached to the infundibular septum by a remnant of the interventricular membranous septum. None had chordal attachments to the septum, that is the bridging leaflet was 'free-floating'. In this group there was variation in the size of the papillary muscle supporting the anterior commissure, between a single large muscle and multiple small muscles. However, all were attached towards the apex, in comparison with the normal medial papillary complex and neither a 'normal' medial muscle nor a trabecula septomarginalis was identified in any cases. The apical muscles all showed a tendency to approximate the anterolateral muscle, were well formed, and supported the commissure between the right anterior and the right lateral leaflets (Fig. 4, 5).

BRIDGING LEFT ANTERIOR LEAFLET TO CONJOINED ANTEROLATERAL MUSCLE (Fig. 1e)

In 17 cases, the left anterior leaflet extended from

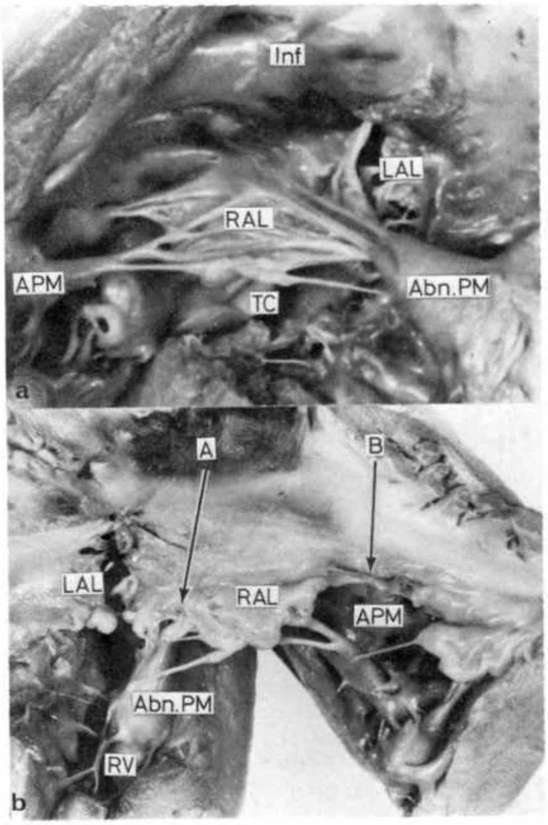

Fig. 4 *Photographs illustrating the morphology illustrated diagrammatically in Fig. 1d. Fig. 4a shows the infundibular view. The left anterior leaflet again bridges the septum but the commissural chord between it and the right anterior leaflet is attached to an abnormal papillary muscle situated on the right ventricular septal surface (Abn. PM). Fig. 4b shows the right posterior view of these leaflets. The left anterior leaflet bridges to a greater extent than in the heart illustrated in Fig. 3. The right anterior leaflet in contrast is smaller than the heart shown in Fig. 3. This specimen had been repaired surgically. The stitches in the left anterior leaflet were for reconstitution of this leaflet. (Other abbreviations as before.)*

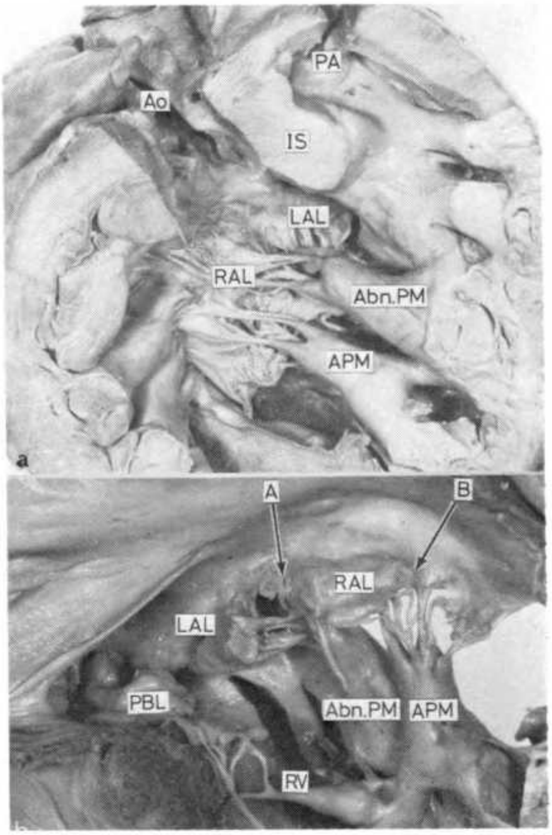

Fig. 5 *Photographs of another heart illustrating the morphology shown diagrammatically in Fig. 1d. In this heart the abnormal papillary muscle supporting the commissure between the anterior leaflets is much closer to the anterior papillary muscle supporting the commissure B between the right anterior and lateral leaflets. Fig. 5a shows the infundibular view and Fig. 5b the right posterior view of this heart. The ventriculoarterial connection was double outlet right ventricle. This is illustrated in Fig. 5a where both the aorta (Ao) and pulmonary artery (PA) are seen arising from the right ventricle, their origins separated by the infundibular septum (IS). (Other abbreviations as before.)*

the left anterolateral papillary muscle of the left ventricle to the anterolateral muscle group of the right ventricle. This muscle group of the right ventricle in all cases was bifid, and supported two discrete commissures. One commissure was formed between the two anterior leaflets, the other between the right anterior leaflet, which was considerably reduced in size, and the right lateral leaflet (Fig. 6, 7). The pattern of the conjoined right anterolateral muscle varied, but two commissural chords were always identified (Fig. 7b). As the left anterior leaflet bridged the septum, it was attached to the infundibular septum by the membranous septal remnant in three cases. In all cases but one the leaflet was unattached with reference to the trabecular septum (free floating). In none of these cases was it possible to identify papillary apparatus comparable with the normal medial papillary muscle complex (Fig. 6, 7).

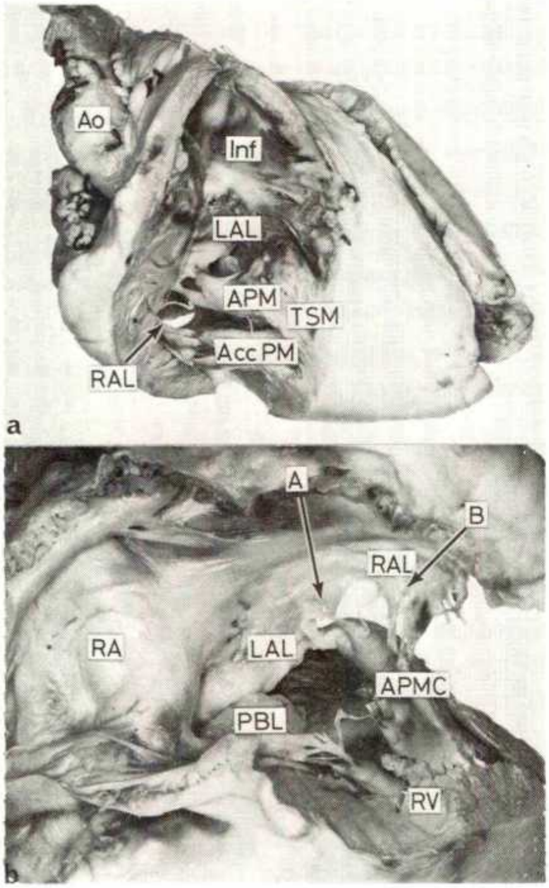

Fig. 6 *Photograph illustrating the morphology shown diagrammatically in Fig. 1e. In this heart the commissures between both the left anterior and the right anterior and between the right anterior leaflet and the right lateral leaflet (commissures A and B) are both supported by the anterior papillary muscle (APM) together with an accessory papillary muscle (Acc PM). When viewed from the posterior aspects (Fig. 6b) these two muscles together form an anterior papillary muscle complex (APMC). The right anterior leaflet is still smaller in this heart and comparison with Fig. 2–5 will illustrate a spectrum of malformations, depending on the position of the papillary muscle supporting commissure A.*

POSTERIOR BRIDGING LEAFLET

In all cases the posterior leaflet was common to both right and left ventricles. In 59 cases, the posterior leaflet was firmly attached at the crux, but became free as it passed anteriorly, part of the ventricular septal defect being beneath the leaflet. However, in no case was the leaflet entirely free

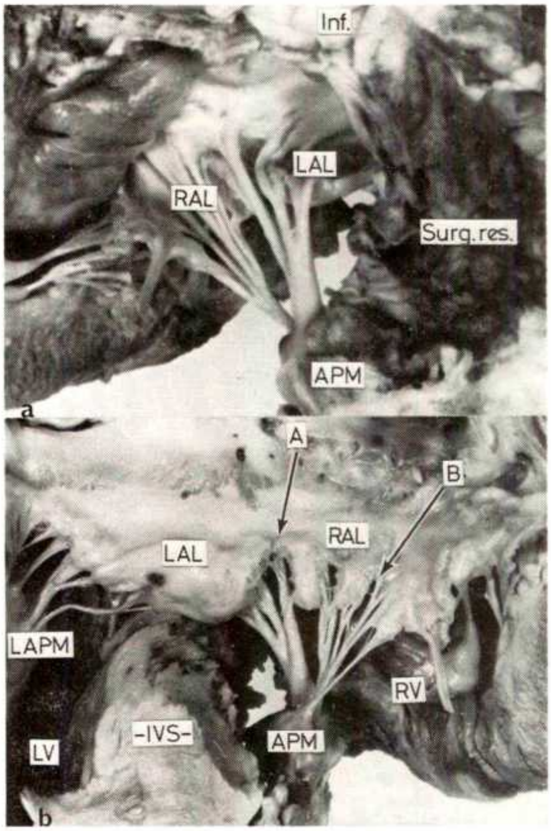

Fig. 7 *Photographs of another heart illustrating the morphology shown diagrammatically in Fig. 1e. In this heart a single anterior papillary muscle supports commissures A and B. The right anterior leaflet is cleft. Fig. 7a is viewed from the infundibulum and Fig. 7b shows a posterior view with transection of the interventricular septum (IVS). There has been surgical resection (Surg res) of the infundibulum in this case.*

floating. In the other 11 cases, the leaflet was firmly attached to the inlet septum throughout its extent. The posterior leaflet always extended between the posteromedial papillary muscle of the left ventricle and the posterior papillary muscle of the right ventricle. There was no correlation between the morphology of the posterior and anterior bridging leaflets.

Discussion

We have described in the previous paper (Piccoli *et al.,* 1979) the basic anatomical features of atrioventricular defects. The cases described here are examples of the complete form. This variety has previously been subdivided according to the variation in leaflet pattern of the anterior components of the common valve and their attachment to the septum. The categorisation of Rastelli *et al.* (1966) into forms with an attached divided anterior leaflet and a free-floating common anterior leaflet, with a rare intermediate form attached to an abnormal papillary muscle, has been found to be of immense value in surgical practice (McGoon *et al.,* 1973; Pacifico and Kirklin, 1973; Alfieri and Subramanian, 1975), though more recently it has been questioned by Berger *et al.* (1978). Furthermore, recent anatomical studies have cast doubt upon the validity of the classification (Goor *et al.,* 1968; Tenckhoff and Stamm, 1973; Goor and Lillehei, 1975; Ugarte *et al.,* 1976).

Our study for the most part endorses the classification of Rastelli *et al.* (1966). However, it differs in several important respects. If the division of anterior leaflets is taken as the commissure between the left anterior and right anterior leaflets, then all examples of complete atrioventricular canal have divided anterior leaflets. Our findings indicate that on the basis of commissural position it is always possible to distinguish two anterior leaflets, two lateral leaflets, and a posterior leaflet. The variation in morphology relates to whether or not the left anterior leaflet bridges the trabecular septum. When it does bridge, then further variation depends on its degree of bridging, its septal tethering, and its papillary muscle attachment.

The largest group in our series showed minimal bridging with septal tethering but attachment to the medial papillary muscle complex. This arrangement was described by Rastelli *et al.* (1966) but their Illustration for this type shows a heart with the left anterior leaflet committed entirely to the left ventricle. We observed only six such hearts in our series. That bridging occurs in the great majority of our hearts is attested to by the attachment of the left anterior leaflet to the medial papillary complex (a feature also observed by Ugarte *et al.,* 1976); in addition, the attachment of the bridging leaflet by chordae to the septal crest, the presence of a membranous septal remnant dividing the left anterior leaflet into left ventricular and right ventricular components, and the attachment of the atrial septum to the left of the anterior commissure are all measures of the degree of rightward extension of the left anterior leaflet.

Increased bridging of the left anterior leaflet was associated in our series with attachment of the anterior commissure to a papillary muscle group situated between the anticipated side of the medial papillary muscle and the anterolateral muscle group. It was significant that in all these cases the normal medial papillary muscle was absent. This group of hearts corresponds with the type B of Rastelli *et al.* (1966), a form whose existence was questioned by Tenckhoff and Stamm (1973) and by Ugarte *et al.* (1976). In these hearts the right anterior leaflet was decreased in size. This trend of increasing bridging and decreasing size of the right anterior leaflet was continued in the hearts observed in which the bridging leaflet was attached to the anterolateral papillary muscle group. Despite attachment to the same muscle group supporting the right anterolateral commissure, in all these hearts it was possible to identify an anterior commissure and to distinguish a small right anterior leaflet. The medial papillary muscle was again absent in these hearts.

Tethering of the bridging leaflet was observed in most but not all the hearts with attachment to the medial papillary muscle. It was also seen in one case with a bridging leaflet. Thus the terms 'attached' or 'unattached' as used by Rastelli *et al.* (1966) are vague. As indicated by Bharati and Lev (1973), attachment can be via chordae to the trabecular septum, via a membranous septal remnant to the infundibular septum, or by commissural attachment to the medial papillary muscle. All of those can coexist. In describing these anatomical findings in complete atrioventricular defects we have not attempted to make deductions about the embryological significance of the observed variations in leaflet morphology and papillary apparatus. From the surgical standpoint it is clear that the cusp tissue available for reconstruction of functional valves must be assessed individually at operation. There seems no reason to believe from our findings that any of the observed variations could preclude surgical repair, provided that both ventricles are of adequate size and sufficient cusp tissue is present. It seems clear, however, that the nature of the defect does imply that anatomically normal valves could not be created and the surgeon should concentrate on finding ways of producing a functionally satisfactory valve rather than attempting to produce facsimiles of the normal mitral and tricuspid valves.

In conclusion, our results suggest that complete atrioventricular defects can be simply divided according to the attachment of the anterior leaflets of the valve, two in number. The differentiation is that the left anterior leaflet may be committed solely to the left ventricle or may bridge the septum to be attached to the medial papillary muscle, an apical papillary muscle, or the anterolateral papillary muscle group of the right ventricle With increased bridging of the left anterior leaflet, there is concomitant decrease in size of the right anterior leaflet.

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Angiocardiographic appearances of atrioventricular defects with particular reference to distinction of ostium primum atrial septal defect from common atrioventricular orifice

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SUMMARY Preoperative distinction between common atrioventricular orifice and ostium primum atrial septal defect may be difficult.

To improve diagnostic accuracy, the right and left ventricular angiocardiograms were reviewed 'blind' in 92 patients with atrioventricular defects. The true diagnosis was known from necropsy or surgery in 60. Angiocardiograms had been obtained in various projections with or without craniocaudal tilt. Those features thought to distinguish between common orifice and ostium primum were coded, together with the ventricular systolic pressures.

Computerised discriminant function analysis identified the following distinguishing features: (1) right ventricular systolic pressure; (2) immediate right ventricular outflow tract opacification from the left ventricle; (3) identification of the anterior attachment of the mitral component; (4) recognition of a single straddling atrioventricular orifice; (5) passage of contrast medium above or below the anterior or posterior bridging leaflets.

Feature (3) indicates that in contrast to classic teaching the direct septal attachment of the mitral component does not contribute to the 'gooseneck' in complete atrioventricular defects. The significance of (4) and (5) is that they may be identified from right as well as left ventriculography, and are more likely to be identified in oblique than standard projections. Computerisation produced a correct diagnosis in 92 per cent of known cases, and determined precise probabilities of diagnosis in the remainder.

The angiographic abnormalities which characterise atrioventricular defects were first described in a classic paper by Baron *et al.* (1964). These authors clearly described the manner in which the abnormal septal attachment of the mitral valve in this condition produces, in the frontal angiocardiogram, the appearance of the 'gooseneck' deformity of the left ventricular outflow tract. It was 10 years before Blieden and his colleagues (1974) correctly pointed out that the deformity present was not simply one of the gooseneck (left ventricular outflow tract) but also of the goose (deficiency of the diaphragmatic wall of the left ventricle), but these authors continued to relate the angiocardiographic appearances to the left ventricular septum rather than to its free wall.

The logic of these arguments seems clear when applied to the partial defect (ostium primum atrial septal defect). However, it was difficult to understand how the same reasoning could be applied to the diastolic appearances of the complete defect (common atrioventricular orifice), since here there is rarely any direct attachment of the bridging anterior atrioventricular leaflet to the crest of the septum. Such a direct attachment is necessary to visualise atrioventricular leaflets angiocardiographically since it is essential to have a pronounced difference in

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opacification of blood on the two sides of the leaflet. Thus, we reasoned that in common atrioventricular orifice, the characteristic radiological appearance should result not from the abnormally positioned septal attachment of the mitral component, as in the ostium primum defect, but rather from its absence. Yet both conditions can present with similar abnormalities of attachment of the mitral component! Since the similarity could not be the result of the septal attachment, the two conditions must have in common an abnormal free wall attachment. But the latter had been almost ignored in the published reports, and when mentioned, had been specifically stated to be normal (Baron *et al.*, 1964; Somerville and Jefferson, 1968). If this reasoning were correct, it would follow that analysis of the type of attachment present would help to distinguish partial from complete defects.

Furthermore, in the complete defect, the absence of direct septal attachments of the anterior leaflet applied to both mitral and tricuspid components. Accordingly, despite the fact that previous attempts to demonstrate abnormalities on right ventricular angiocardiography had failed, apart from showing non-specific tricuspid regurgitation (Baron *et al.*, 1964; Rastelli *et al.*, 1967), we reasoned that they must indeed exist.

Finally, as many of the points of preoperative differentiation between ostium primum atrial septal defect and common atrioventricular orifice are suggestive, but not specific (Rastelli *et al.*, 1967), it seemed that computer-assisted diagnosis using multivariate analysis might improve accuracy.

With these considerations in mind, we studied the angiocardiograms of the 92 patients with atrioventricular defects who had been investigated since 1967.

Subjects and methods

All patients reported had undergone cardiac catheterisation, and all but two had also had selective left ventriculography at The Hospital for Sick Children over the past 10 years. The diagnosis of either ostium primum atrial septal defect or common atrioventricular orifice had been established either by angiocardiography, at open-heart surgery (45 patients who survived), or at necropsy (15 patients). Thus in 60 patients (65·2%) there was independent confirmation of the angiocardiographic diagnosis. Patients with rarer forms of partial defects, such as inlet ventricular septal defect with cleft mitral valve and intact atrial septum, were excluded, as were those with a univentricular heart. Common atrioventricular orifice was defined as that condition in which there was no continuity over the septal crest between the anterior and posterior leaflets, whereas in ostium primum atrial septal defect leaflet continuity at this point divided the atrioventricular canal into separate mitral and tricuspid valves (Wakai and Edwards, 1958; Bharati and Lev, 1973). The terminology employed by Piccoli *et al.* (1979a, b) will be used throughout to describe the anatomical features.

The angiocardiograms were all reviewed by one observer (FJM), without knowledge of the patient's name, diagnosis, or haemodynamic status. In a small proportion of cases, this analysis could not have been completely blind, because the angiocardiogram was recognised as belonging to a recently investigated patient, but as many of such patients had not yet undergone open-heart surgery, the analysis was truly blind in at least 90 per cent of cases.

Particular note was paid in all films to the appearance of the annulus of a common valve or the mitral and tricuspid valve annuli as seen during diastole. Diastole was easily identified on cine angiocardiograms, but had to be inferred from the state of the atrioventricular and semilunar valves on large film angiocardiograms taken at six per second.

In anteroposterior projections, the *septal* (anterior) attachment of the mitral valve was regarded as identified with certainty if a *diastolic cleft* was seen, that is a fine jet of non-opacified blood entering the left ventricular cavity during protodiastole, before full opening of the mitral valve. The site of this cleft invariably corresponded with the site of the systolic jet of mitral regurgitation, if present.

The *free wall* (posterior) attachment of the mitral valve or mitral component of the common atrioventricular valve was regarded as positively identified if the left circumflex coronary artery was seen in close relation to it throughout at least 80 per cent of its length. In left anterior oblique projections, with (Bargeron *et al.*, 1977; Elliott *et al.*, 1977; Rees *et al.*, 1978) and without (Brandt *et al.*, 1972; Brandt, 1973) craniocaudal tilt, the distinction of free wall from septal attachment is obvious as the projection is chosen in order to separate the left ventricular septum from its free wall. Nevertheless, the relation between the circumflex artery and the free wall attachment was noted. Craniocaudal tilt was obtained by raising the patient's shoulders so as to bring the thorax to 45° from the table top, and then rotating the left shoulder forward through 30°. Craniocaudal tilt is strictly only applied to the projection obtained with the vertical tube and camera, but the simultaneously exposed view in the horizontal plane at right angles to the long axis of the table is loosely referred to as right anterior oblique with craniocaudal tilt.

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Where a single, complete, undivided ring of atrioventricular leaflet attachment was visualised overriding the trabecular (muscular) interventricular septum, the angiocardiogram was held to demonstrate a common atrioventricular orifice.

The atrioventricular annulus or annuli are not the only structures which produce a sharp diastolic interface between opacified and non-opacified blood. The leaflets themselves also produce this appearance. On cine angiocardiography leaflets are easily distinguished from annuli by their rapid movement and particularly by the 'M' shaped flutter so well known to echocardiographers. However, it is also apparent from cine angiocardiograms that leaflets tend to be straighter than annuli, and this provides a means of distinguishing the two on large film angiocardiograms taken at six per second. The relation between the anterior mitral (or common anterior) leaflet and the left ventricular line of attachment of the valve was noted particularly on frontal angiocardiograms.

In systole, attention was paid to the presence of filling of the right ventricular outflow tract on the first systole, and to demonstration of the passage of contrast medium from either ventricle to the other above or below a bridging left anterior, separate left and right anterior, or a bridging posterior leaflet of the common atrioventricular valve. In addition, evidence of a filling defect in the presumed region of the mitral valve was sought, and the presence or absence of a systolic gooseneck deformity of the left ventricular outflow tract was noted.

It became apparent that there was no possibility of identifying the varieties of papillary muscle attachment of the left anterior leaflet angiocardiographically in common atrioventricular orifice, but an attempt was made, in the light of the operative or necropsy diagnosis, to distinguish anterior or posterior leaflets attached by chordae tendineae to the crest of the ventricular septum from those which were 'free-floating' (Rastelli *et al.*, 1966).

These observations were then coded, punched onto cards, and analysed at The University of London Computer Centre, using the *Statistical Package for the Social Sciences* for cross-tabulation and discriminant function analysis (Nie *et al.*, 1975). Stepwise entry of variables into the discriminant equation was assessed by their ability to minimise Wilks' lambda. Classification was weighted according to the proportion of patients in each known diagnosis category. The discriminant functions were based upon the 60 patients with independent confirmation of the diagnosis, and then applied to the remaining 32, so as to give a haemodynamic/angiocardiographic diagnosis, together with a probability of its being correct. It is this probability that is quoted in the figure legends.

Results

Only selective right and left ventricular angiocardiograms were analysed. In all, 151 films were reviewed, 137 (90·7%) of these having been taken in two planes at right angles to one another. Table 1 gives details of the injections and projections used.

Table 1 *Ventricular angiocardiograms in 92 patients*

Projection(s) of left ventricular angiocardiogram	*Film type*	*Independent confirmation of diagnosis*	*No independent confirmation of diagnosis*
Posteroanterior/lateral only	Roll film	18 (9)*	10 (5)
Anteroposterior/lateral only	Cine	16 (4)	12 (6)
Right ventricular anteroposteror/lateral only	Cine	(2)	0
Left anterior oblique/right anterior oblique only	Cine	2 (1)	2 (1)
Left anterior oblique/right anterior oblique + craniocaudal tilt	Cine	6 (3)	3 (1)
Posteroanterior/lateral *and* left anterior oblique/right anterior oblique	Roll film, Cine	3	3
Anteroposterior/lateral *and* left anterior oblique/right anterior oblique	Cine Cine	9 (3)	0
Anteroposterior/lateral *and* left anterior oblique/right anterior oblique + craniocaudal tilt	Cine Cine	3 (3)	2
Anteroposterior/lateral *and* left anterior oblique/right anterior oblique *and* left anterior oblique/right anterior oblique + craniocaudal tilt	Cine Cine Cine	1 (1)	0
		60	32
Right ventricular posteroanterior/lateral	Roll film	10	5
Right ventricular anteroposterior/lateral	Cine	16	8
		26	13

*Parentheses indicate number who also had an RV angio of any type (invariably biplane in frontal and lateral projections). In 14 of the 151 films(9·3%) the films were in only one projection, but the details have been omitted for simplicity. Two were lateral films only, six craniocaudal tilt, and six left anterior oblique only.

In brief, 39 (25·8%) were right ventricular angiocardiograms in the frontal and lateral planes. In 112 (74·2%), injection was into the left ventricle. Seventy-seven (68·8%) left ventricular angiocardiograms were in the frontal or lateral projections, and 35 (31·2%) were in oblique projections, to which craniocaudal tilt had been added in 15.

IDENTIFICATION OF ANTERIOR AND POSTERIOR ATTACHMENTS OF MITRAL VALVE (OR COMPONENT) (Table 2)

A diastolic cleft was identified in five frontal cine angiograms and 17 frontal roll films. The line of attachment associated with this diastolic cleft was invariably puckered (Fig. 1A cf. with Fig. 1C, 2A).

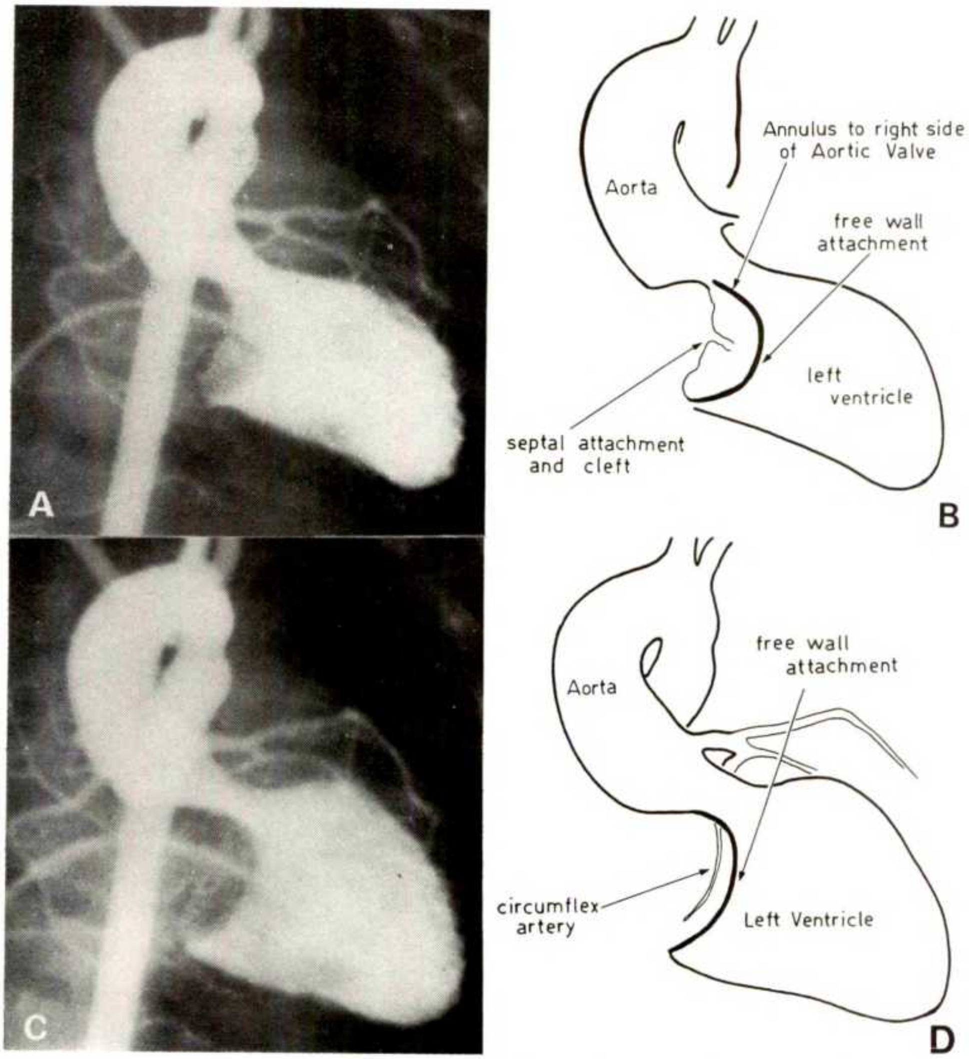

Fig. 1 *Frontal left ventricular angiocardiogram. Two diastolic frames from a patient with ostium primum atrial septal defect ($P=0·997$). Note that a 'gooseneck' deformity is present in A and C. However in C it is formed by the smooth free wall mitral valve attachment alone, whereas two 'goosenecks' are visible in A. That formed by the free wall attachment is still visible, but the most prominent is due to the classical appearance of the septal attachment, marked by puckering and a diastolic cleft. The circumflex coronary artery is faintly seen in C immediately medial to the free wall attachment.*

Table 2 *Left ventricular frontal cine angiocardiograms in patients with independent confirmation of diagnosis*

	Ostium primum	*Common AV orifice*
Anterior attachment seen		
(diastolic cleft and puckering)	5 } 7	0
(puckering only)	2 }	0
Anterior attachment not seen	8	13
Posterior attachment seen (LCCA, smooth)	9 } 15	7 } 13
(smooth only)	6 }	6 }
Posterior attachment not seen	0	0

N.B. There was one lateral cine with no frontal cine.
P for visualisation of anterior attachment = 0·01.
LCCA, left circumflex coronary artery.

The left circumflex coronary artery was identified lying immediately medial to the posterior attachment of the mitral valve in 36 frontal and 10 left anterior oblique films. The posterior line of attachment was invariably smooth, in contrast to the anterior attachment (Fig. 1A and B). We concluded that a puckered attachment is anterior and a smooth attachment is posterior even if the diastolic cleft and left circumflex coronary artery are not seen.

In only four films (2·6%) was no posterior line of attachment seen. Whether identified in the frontal or left anterior oblique projection, with or without craniocaudal tilt, the inferior end of the posterior attachment was always displaced apically by comparison with the normal posterior line of attachment (Fig 2, 3, 9). This apical displacement was occasionally subtle, but usually obvious. Since the posterior and anterior lines of attachment are continuous with one another, this displacement applied equally to the anterior attachment, when present.

Superiorly, the posterior line of attachment of the mitral valve as seen in the frontal projection was also abnormal. Whereas in the normal patient the posterior attachment becomes continuous with the lateral free wall of the left ventricle before running

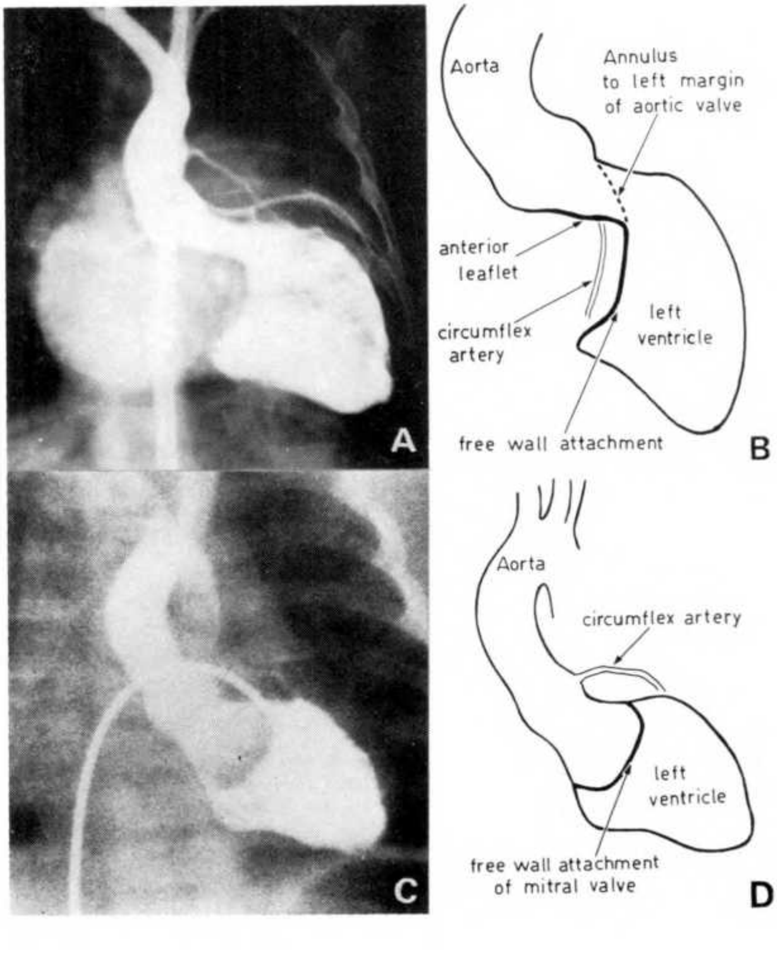

Fig. 2 *Comparison of diastolic frontal angiocardiogram from patient with normal mitral valve (C) and one with ostium primum atrial septal defect (A) (P = 0·998). In both, the free wall attachment is clearly seen. Note inferiorly, the apical displacement of the free wall attachment in A. However, the most striking abnormality is superior. While in the normal (C), the region of non-opacified blood entering the left ventricle runs all the way from the free wall attachment to the aortic valve, in atrioventricular defects (A), there is a heavily opacified 'tunnel' (the 'gooseneck') consisting of contrast medium above the anterior mitral leaflet. Note the absence of demonstration of the septal attachment, and the angulation between anterior mitral leaflet and free wall attachment.*

onto the left coronary cusp of the aortic valve (Fig. 2C, D), in these patients with atrioventricular defects, though the posterior line of attachment could sometimes be seen to merge normally with the leftward margin of the aortic valve (Fig. 2A, B), it occasionally ran up to the middle of the valve, and more frequently apparently to the right side of the valve (Fig. 1). The word 'apparently' is used because the anterior mitral (or common leaflet) also hinges on the rightward margin of the aortic valve, and it is difficult on roll films to distinguish between leaflet and annulus at this point. However, whatever the precise reason for this appearance, the fact remains that whereas in the normal frontal left ventricular angiocardiogram the ring of non-opacified blood entering during diastole runs up to the whole width of the aortic valve (Fig. 2C), in atrioventricular defects there is a wedge of contrast medium separating the left margin of the aortic valve from the non-opacified blood entering the left ventricle (Fig. 1, 2A). This forms the diastolic gooseneck deformity.

When present, that is in ostium primum defects, the anterior attachment normally lay more or less directly anterior to the posterior attachment, both in its upper region where it approached horizontal, and more caudally where it approached vertical (Fig. 1A).

In *left anterior oblique projections,* with or without craniocaudal tilt, even if the detail of the posterior attachment of the mitral valve (or component) was partially obscured by preceding mitral regurgitation, non-opacified blood (and indeed a cardiac catheter) was seen to enter the left ventricle from a highly

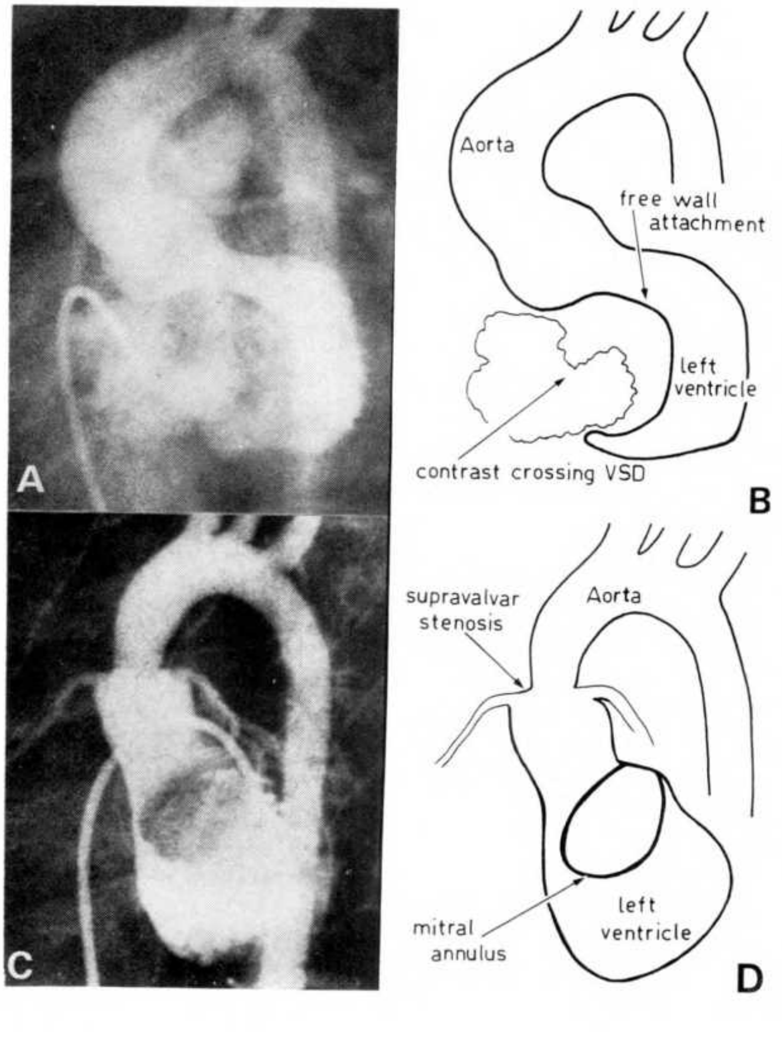

Fig. 3 *Comparison of appearances of diastolic left anterior oblique left ventricular angiocardiograms in patient with normal mitral valve (C) and common atrioventricular orifice (A) ($P = 0{\cdot}986$). Note that in the atrioventricular defect (A), the mitral annulus seems to spring from the septum anteriorly, whereas the normal mitral annulus (C) only makes tenuous contact with the ventricular septum. No septal attachment of the mitral valve is seen in (A); instead contrast medium has in the previous systole crossed the entire common orifice to opacify the right ventricle, and hence the pulmonary atery. The patient in (C) had supravalvar aortic stenosis in association with the idiopathic hypercalcaemia syndrome. Note that the catheter appears to enter the left ventricle in this projection from behind when the mitral valve is normal, but from in front in atrioventricular defects.*

abnormal direction, that is from above and in front of as opposed to above and behind the left ventricle, as viewed in this projection (Fig. 3). In the lateral view, while the mitral annulus was seen to be abnormally anterior in a few patients, the diastolic appearances were in general not diagnostic.

SYSTOLIC APPEARANCES—GENERAL COMMENTS

The majority of angiocardiograms were obtained with the catheter through the mitral valve (or component), which exacerbated the usual (but not invariable) mitral regurgitation. The left anterior oblique projection with craniocaudal tilt separates left from right atrium well, and it was clear that the jet of mitral regurgitation was directed largely or entirely into the right atrium in all patients.

Because of mitral regurgitation, opacification on either side of the mitral leaflets tended to equalise, more so in systole than in diastole. The resultant loss of definition meant that systolic appearances were in general far less diagnostic of atrioventricular defects than diastolic appearances. While the systolic gooseneck deformity of the left ventricular outflow tract in the frontal projection was frequently seen, it was just as frequently not present. However, ballooning of mitral valve tissue anterior to the left ventricular cavity in the lateral projection is, when seen, diagnostic (Fig. 4A) as is the corresponding appearance in the left anterior oblique projection (Fig. 4C) with or without craniocaudal tilt.

Careful study of cineangiocardiograms showed a systolic 'cleft' in nine patients, which presumably represented apposition of the thickened leaflet margins in the region of the cleft (Fig. 4C). The same appearance was present in many roll films, though here it was more difficult to be sure that the film was systolic.

RIGHT VENTRICULAR ANGIOCARDIOGRAMS—GENERAL APPEARANCES

In only 15 films (38·5%), one of which was in the lateral projection only, was the tricuspid valve (or component) indistinguishable from normal. The most subtle abnormality was shifting of the annulus leftwards, which progressed to the obviously abnormal situation in which the tricuspid valve appeared in the frontal projection to spring from the lateral margin of the right ventricle. A particularly interesting example is shown in Fig. 5. This patient had a bidirectional shunt at atrial level and was clinically cyanotic in the presence of a normal right ventricular pressure and the absence of a common atrium or anomalous systemic drainage. At operation an ostium primum defect was closed uneventfully. The cause of the atrial right-to-left shunt was hypoplasia of the tricuspid valve and right ventricle. The frontal angiocardiograms (Fig. 5) in this patient in fact show distinct leftward displacement of both tricuspid and mitral free wall attachments resulting in an abnormally large mitral and an abnormally small tricuspid orifice. This anatomy corresponds, in an ostium primum defect, to the dominant left ventricle variety of the complete defect as described by Bharati and Lev (1973).

The abnormalities on right ventricular angiocardiography are pertinent to the next section and will be discussed there.

DIFFERENTIATION OF OSTIUM PRIMUM ATRIAL SEPTAL DEFECT FROM COMMON ATRIOVENTRICULAR ORIFICE

This section is based, unless stated otherwise, upon the 60 patients in whom independent confirmation of the diagnosis was available.

Direct recognition of common atrioventricular orifice

This was the single most informative angiocardiographic sign. Table 3 demonstrates that it was never seen in cases of ostium primum. It was more common in the presence of 'free-floating' anterior leaflets than attached ones in the presence of a common orifice, though not to a statistically significant degree. This appearance was seen in all projections used apart from right anterior oblique, and with injection into either ventricle. The common orifice was circular or ovoid in shape, or sometimes rhomboidal, with the short parallel side lying superiorly (Fig. 6). It straddled the ventricular septum, but in contrast to the majority of cases of straddling atrioventricular valves without common atrioventricular orifice (Liberthson *et al.*, 1971), no second atrioventricular orifice was demonstrated.

This sign was seen in a further 10 patients without independent confirmation of the diagnosis. In only eight of 20 (26·7%) was a common orifice demonstrated on both right and left ventricular angiocardiograms. Indeed in 26·7 per cent this appearance was seen on selective right ventricular, but not selective left ventricular angiocardiography; that is the diagnosis of common orifice was established despite left ventricular angiocardiography. However, in four of 30 patients (13·3%), a common orifice was seen on left ventricular, but not right ventricular angiocardiography. These differences were largely the result of the direction of the dominant shunt at ventricular level, and are summarised in Table 4.

Of particular importance to the choice of projection used is the incidence of identification of common orifice related to the projection of left ventricular angiocardiography used (Table 5). In 14 of 18 (77·8%) frontal or lateral angiocardiograms, no common orifice was shown though it was known that it existed. By contrast, this failure to demonstrate a common orifice when present occurred in only two of 11 (18·2%) left anterior oblique angiocardiograms with and without craniocaudal tilt.

These differences could not be explained by differences in the underlying diagnosis. It seems clear that oblique projections are more likely to show a common orifice if it in fact exists.

Systolic traverse of contrast medium across different components of the common orifice

It was often possible, with injection into either the right or left ventricle, particularly in oblique

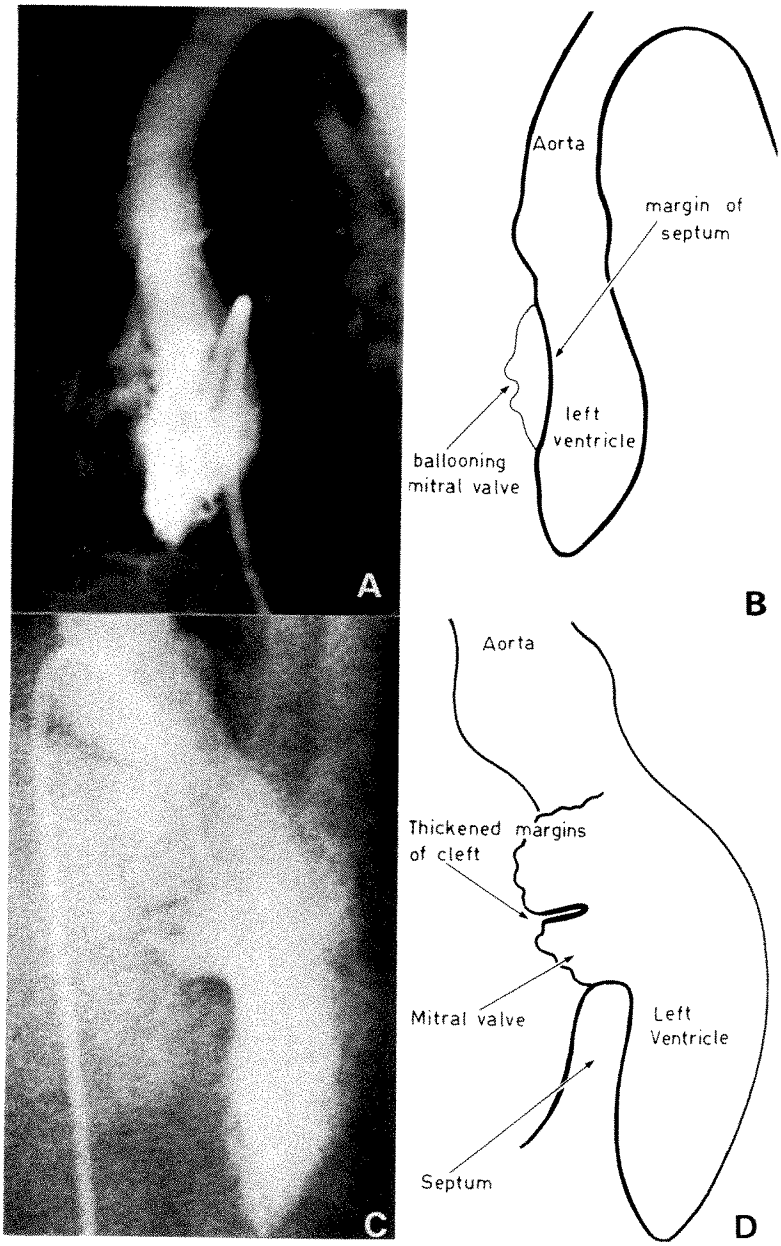

Fig. 4 *Systolic appearances of mitral valve. (A) Lateral projection, ostium primum atrial septal defect (operative diagnosis). The mitral valve balloons anterior to the left ventricular cavity. This patient also had a cor triatriatum (not seen on this frame). (C) Left anterior oblique projection with craniocaudal tilt. Ostium primum atrial septal defect (operative diagnosis). It can clearly be seen that the mitral valve is firmly attached to the crest of the septum. It balloons toward the right atrium.*

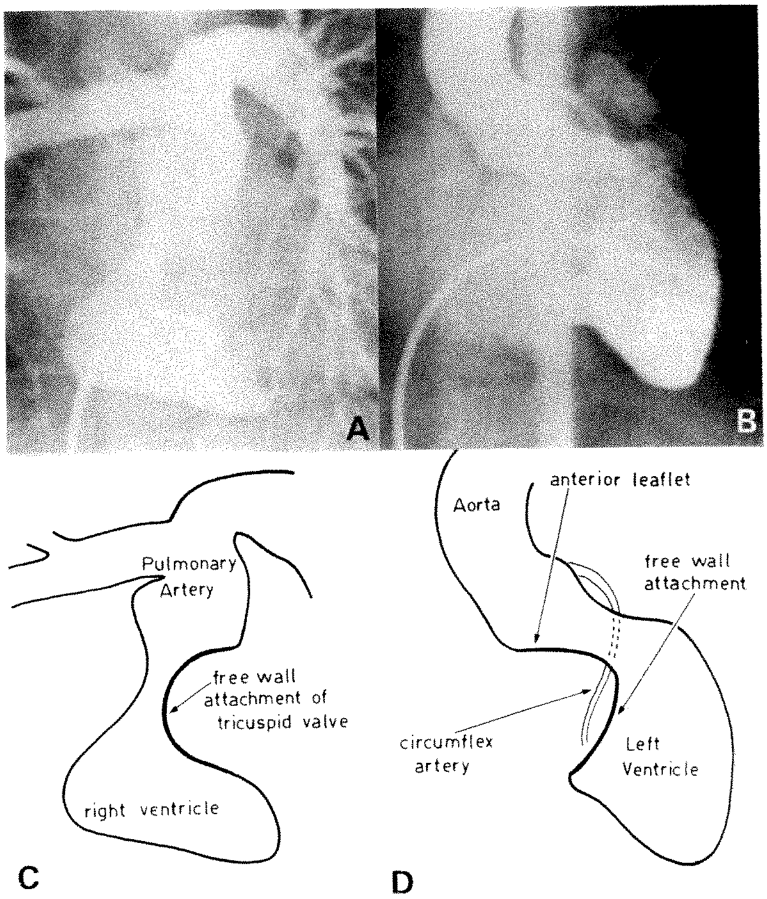

Fig. 5 *Ostium primum atrial shunt because of right ventricular and tricuspid valve hypoplasia (operative diagnosis). Frontal projections of right (A) and left (B) ventricular angiocardiograms. Note the leftward displacement of both free wall annuli, giving an unusually large mitral annulus. Note also the sharp angulation between anterior mitral leaflet and the free wall attachment of the mitral valve, as in Fig. 2A.*

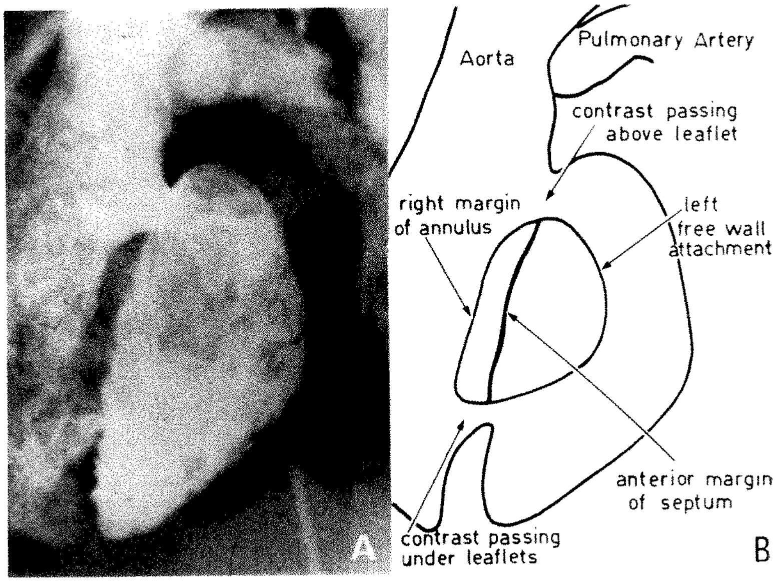

Fig. 6 *Common atrioventricular orifice (P = 1·00). This patient also had inversus—concordant—double outlet right ventricle with pulmonary stenosis and dextrocardia. This lateral left ventricular angiocardiogram in diastole shows a rhomboidal common atrioventricular orifice straddling the ventricular septum. Both great arteries originate from the right ventricle.*

Table 3 *Significance of direct angiocardiographic demonstration of common AV orifice in 60 patients with independently confirmed diagnosis*

	Common AV orifice visualised *No*	*Yes*	*Total*
Ostium primum	29 (100%)	0	29
Common AV orifice—'attached' anterior leaflet	9 (50%)	9 (50%)	18
Common AV orifice—'free' anterior leaflet	2 (14·4%)	11 (84·6%)	13
Total	40	20	60

$\chi=32{\cdot}1$ $P<0{\cdot}0001$

projections, to identify contrast medium crossing above the anterior bridging leaflet or leaflets or below the posterior bridging leaflet during systole (Fig. 7). One disadvantage of craniocaudal tilt was that it became extremely difficult to recognise contrast medium passing above the anterior leaflet, because this critical region overlapped the usually opacified atria and origin of the great arteries. In other cases a broad band of contrast medium clearly crossed from one ventricle to the other throughout the width of the atrioventricular orifice (Fig. 3A). These signs were never seen in ostium primum, but occurred in

Table 4 *Site of selective ventricular angiocardiogram compared with visualisation of common AV orifice*

	Common AV orifice on LV angio	*LV angio done; no common AV orifice*	*No LV angio*
Common AV orifice on RV angio	8	8	2
RV angio done; no common AV orifice seen	4	—	—
RV angio not done	8	—	—

Table 5 *Projections in which common AV orifice identified on LV angiocardiograms*

Angio finding *Independent diagnosis* *Projection*	*Common AV orifice seen* *Common AV orifice*	*Not known*	*Common AV orifice not seen* *Common AV orifice*
Frontal	4*	2	14
Lateral	3†	0	
Left anterior oblique without craniocaudal tilt	7	1	1
Left anterior oblique with craniocaudal tilt	2	1	1

*two also seen in lateral but not included there.
†two also seen in other projections (one frontal and left anterior oblique, one left anterior oblique only) but not included in left anterior oblique.

Table 6 *Systolic traverse of atrioventricular orifice above anterior leaflet, below posterior leaflet, or across whole width*

	No	*Yes*	
Ostium primum	29 (100%)	0	29
Common AV orifice—'attached' anterior bridging leaflet	7 (38·9%)	11 (61·1%)	18
Common AV orifice—'free' anterior bridging leaflet	3 (23·1%)	10 (76·9%)	13
	39	21	60

$\chi^2=31{\cdot}05$ $P<0{\cdot}0001$

Table 7 *Right ventricular outflow tract opacification from left ventricle on first systole*

	LV outflow tract opacification *No*	*Yes*	*Uncertain*	
Ostium primum	16 (55·2%)	3 (10·3%)	10 (34·5%)	29
Common AV orifice—'attached' anterior bridging leaflet	1 (5·6%)	12 (66·7%)	5 (27·8%)	18
Common AV orifice—'free' anterior bridging leaflet	0 (0%)	11 (84·6%)	2 (15·4%)	13
	17	26	17	60

$\chi^2=30{\cdot}2$ $P<0{\cdot}0001$

67·7 per cent of cases with common orifice, there being no significant correlation within the latter group with the type of attachment of the common leaflets (Table 6). In certain instances the presence of systolic traverse was most easily confirmed with the onset of the next diastole, since contrast medium was then seen trapped behind the leaflet.

Chamber opacified with first ventricular systole
As expected, it was more likely for immediate filling of the right ventricular outflow tract from a left ventricular angiocardiogram to occur with common orifice than with ostium primum, but in many cases, particularly where only frontal and lateral planes had been exposed, it was extremely difficult, even on cine angiocardiograms, to distinguish right atrium from ventricle. In three cases of ostium primum, immediate right ventricular outflow tract filling was confidently (but presumably erroneously) diagnosed (Table 7).

Table 8 *Relation between diagnosis and RV systolic pressure*

	RV systolic pressure (mmHg)					
	<40	*40–60*	*60–80*	*80–100*	*>100*	
Ostium primum	13 (44·8%)	8 (27·6%)	8 (27·6%)	0	0	29
Common AV orifice—'attached' anterior bridging leaflet	1 (5·6%)	3 (16·7%)	5 (27·8%)	8 (44·4%)	1 (5·6%)	18
Common AV orifice—'free' anterior bridging leaflet	1 (7·7%)	2 (15·4%)	4 (30·8%)	6 (46·2%)	0	13
	15	13	17	14	1	60

$\chi^2 = 25{\cdot}22$ $P = 0{\cdot}0014$

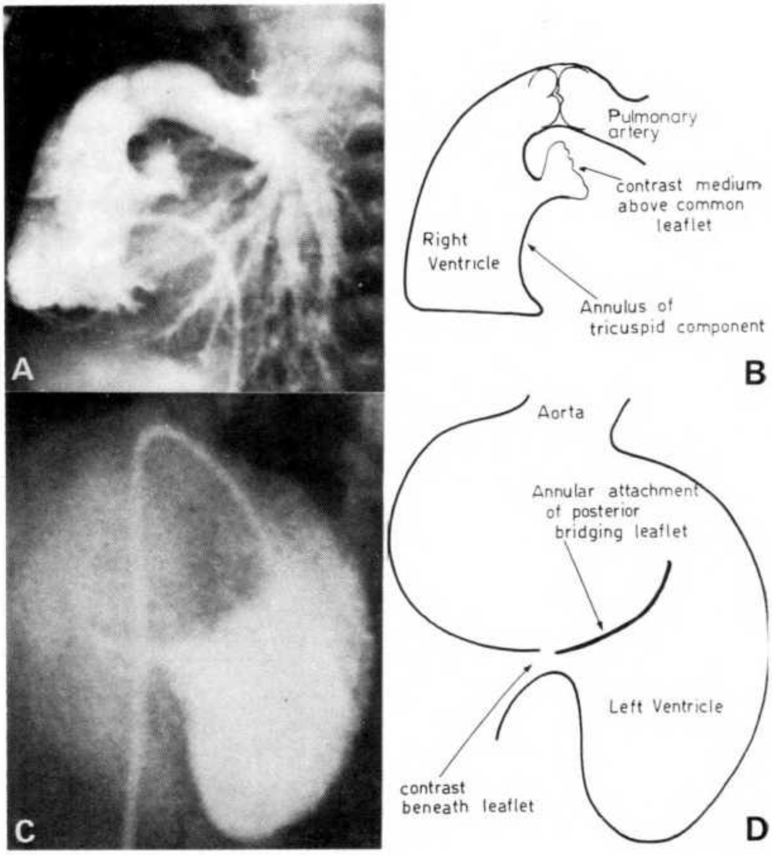
A
Pulmonary artery
contrast medium above common leaflet
Right Ventricle
Annulus of tricuspid component
B
Aorta
Annular attachment of posterior bridging leaflet
Left Ventricle
contrast beneath leaflet
C
D

Fig. 7 *Systolic traverse above and below bridging leaflets. In both angiocardiograms the films actually shown are in early diastole so as to show the valve annulus, but contrast medium passed to the position shown in the preceding systole.*
(A) Lateral projection, right ventricular angiocardiogram. Contrast medium is crossing above the anterior bridging leaflet. The patient had a right-to-left shunt caused by severe pulmonary vascular obstructive disease. At necropsy, neither bridging leaflet was attached to the ventricular septum, and the anterior bridging leaflet was supported on the right side by a conjoined anterolateral papillary muscle only.
(C) Left ventricular angiocardiogram, left anterior oblique position with craniocaudal tilt. Contrast medium has passed beneath the posterior bridging leaflet. At operation both bridging leaflets were attached by short chordae tendineae to the crest of the ventricular septum.

Relation with ventricular systolic pressures

It was possible to establish a significant correlation between anatomical diagnosis and either right ventricular systolic pressure alone or its ratio with left ventricular pressure. However, despite the wide age range of patients (from 1 day to14 years) the correlation was no better for pressure ratio than for absolute right ventricular peak systolic pressure. Thus, for brevity, the latter only is presented (Table 8). The right ventricular systolic pressure was below 80 mmHg in all cases of ostium primum, and 60 mmHg or above in 24 (77·4%) cases of common orifice.

Table 9 *Value code for variables in discriminant function*

RV systolic pressure (mmHg) (RVR)
1=<40 2=40=59 3=60–79 4=80–99 5=>100
Common AV orifice (CAVO) visualised angiocardiographically (CAVO) 0=no 1=yes.
Systolic jet above or below anterior or posterior leaflets, or across width of AV orifice (SYSJET) 0=no 1=yes.
Immediate RV outflow tract filling from LV injection (RVOT) 0=no 1=uncertain 2=yes
Anterior attachment mitral valve seen (ANTACH) 0=no 1=yes
Systolic jet above anterior leaflets or left anterior bridging leaflet (ABL) 0=no 1=yes'
Systolic jet across width of AV orifice (ACROSS) 0=no 1=yes.
Systolic jet beneath posterior bridging leaflet (PBL) 0=no 1=yes

Table 10 *Discriminant function analysis*

Seven variables

Step number	*Variable entered*	*I to enter*	*Wilks lambda*	*Significance of entry*	*Unstandardised disc. coeff.*	*Standardsed disc. coeff.*
1	RVOT	54·0	0·518	P<0·001	−0·66	−0·56
2	RVR	20·6	0·380	P<0·001	−0·57	−0·66
3	CAVO	7·1	0·337	P<0·001	−1·02	−0·49
4	ANTACH	2·0	0·325	P<0·001	+0·52	+0·25
5	ABL	1·4	0.317	P<0·001	−1·29	−0·50
6	ACROSS	3·5	0·300	P<0·001	−0·94	−0·32
7	PBL	0·7	0·294	P<0·001	+0·57	+0·20
					(constant = +2·66)	

Canonical correlation = 0·841. $\chi^2 = 67{\cdot}9$. DF=9.

Four variables

Step number	*Variable entered*	*F to enter*	*Wilks lambda*	*Significance of entry*	*Unstandardised disc. coeff.*	*Standardised disc. coeff.*
1	SYSJET	58·9	0·496	P<0·001	−1·09	−0·523
2	RVR	16·1	0·387	P<0·001	−0·53	−0·610
3	RVOT	9·4	0·331	P<0·001	−0·75	−0·632
4	CAVO	3·1	0·313	P<0·001	−0·88	−0·417
					(constant = +2·88)	

Canonical correlation = 0·829. $\chi^2 = 66{\cdot}1$. DF=4.
Abbreviations of variables as in Table 9. DF, degrees of freedom; disc. coeff., discriminant coefficient.

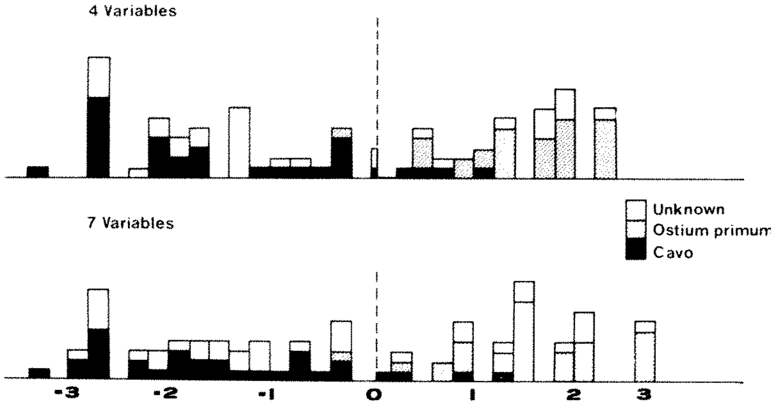

Fig. 8 *Histogram of the discriminant scores for each patient, using the four or seven variables listed in Table 10. The dotted line represents the computer derived line of distinction between the diagnosis, with common atrioventricular orifice to the left and ostium primum atrial septal defect to the right. Discrimination with seven variables produces slightly better separation, with one less misclassification.*

DISCRIMINANT FUNCTION ANALYSIS

This was originally carried out with inclusion of all the variables detailed, together with actual rather than coded right ventricular systolic pressure ratio. Though in fact all variables considered were at one stage admitted by the stepwise discrimination at a statistically significant level, discrimination on seven variables separated the two groups common orifice and ostium primum best, as judged by the criteria of minimising Wilks' lambda and maximising canonical correlation. This discriminant function has been used to calculate probabilities of diagnosis for the patients without independent confirmation of diagnosis illustrated in the paper. However, from the practical point of view, discrimination on four variables alone is almost as effective. Fig. 8 and Table 10 compare these discriminants, and Table 9 gives the coding of the variables concerned. Both discriminants incorrectly diagnosed ostium primum in the presence of common orifice in four patients. In each of these four the anterior and posterior leaflets were attached to the crest of the ventricular septum; three only had frontal and lateral left ventricular angiocardiograms. In one patient with an ostium primum, common orifice was incorrectly diagnosed presumably because of an associated large trabecular septal defect. A correct diagnosis was achieved in 91·7 per cent of known cases. The standardised discriminant function coefficients (Table 10) are weighted in such a way as to eliminate the effect of differences in span of the variables concerned, and therefore give a good picture of the relative importance of each factor as a discriminant. It is clear that the most important are the right ventricular systolic pressure and immediate right ventricular outflow tract filling. The diastolic appearance of common orifice and anterior attachment of the mitral valve, and a systolic jet across the atrioventricular orifice are less important since, when present, they are informative, but when absent, less so.

In short, when the sum:—

2·88 − (1·09 × value for SYSJET) − (0·53 × value for RVR) − (0·75 × value for RVOT) − (0·88 × value for CAVO)

exceeds 0·05, the values being as coded in Table 9, the likely diagnosis is ostium primum. When that sum is negative, or positive and less than 0·05, the likely diagnosis is complete atrioventricular canal.

At no stage was a significant second discriminant function obtained which would divide common orifice into different diagnostic categories in addition to separating it from ostium primum.

Discussion

Previous angiocardiographic descriptions of atrioventricular defects have concentrated almost exclusively on the abnormal septal 'attachment' of the mitral valve (Baron *et al.*, 1964; Girod *et al.*, 1965; Rastelli *et al.*, 1967; Gotsman *et al.*, 1968; Somerville and Jefferson, 1968; Tenckhoff and Stamm, 1973; Blieden *et al.*, 1974; Rastelli *et al.*, 1976). The free wall attachment as seen in the frontal plane has either been ignored or dismissed as normal (Baron *et al.*, 1964; Somerville and Jefferson, 1968). Rastelli and colleagues (1967) correctly identified the line of attachment of the mural (left lateral) leaflet in a patient with a 'free-floating anterior common leaflet' and further recognised the importance of the fact that the 'anterior common leaflet' was not attached to the septum, but concluded that the resulting appearance was characteristic of this particular variety of complete defect. Other forms of complete defect with indirect attachment of anterior leaflet tissue to the septal crest were held to show the same angiocardiographic abnormality as was present in ostium primum.

In considering the radiographic appearances of other forms of congenital mitral anomalies (Macartney *et al.*, 1976), we had taken as fundamental the principle that sharp interfaces between opacified and non-opacified blood appearing with each diastole and disappearing with each systole could only be the result of valve leaflets and the annuli to which they attached (rarely, an aneurysm of the interventricular septum may behave in the same way). The common orifice of a complete atrioventricular defect is surrounded by a common annulus, the free wall attachment. A septal annulus only exists in so far as leaflet tissue is attached directly to the septum, and is therefore present in ostium primum but absent or else grossly deficient in complete defects. If, therefore, the appearances of complete defects are interpreted as the result of an abnormally positioned septal attachment, either the theory, the interpretation, or both, must be incorrect. The evidence here presented strongly supports the theory, but may also explain why problems with interpretation, self-evidently present, have occurred.

Observation of the diastolic cleft, which marks the septal mitral attachment in ostium primum, and the circumflex left coronary artery, which marks the free wall attachment, has enabled these two to be distinguished, and has led to two further points of distinction. The septal attachment is puckered, because it is abnormal, and associated with numerous very short chordae running from the crest of the septum to the medial aspect of the anterior and posterior leaflets. The free wall attachment is smooth, as it normally is.

Having established these fundamentals, it is then possible to compare the position of the annulus in atrioventricular defects with that in patients with normal mitral valves. The region of mitral/aortic continuity provides a reference point, though it is not in fact fixed, because in atrioventricular defects the aortic valve has not reached its normal position wedged between the mitral and tricuspid valve. It is too anterior and too far to the right relative to both valves (Piccoli *et al.,* 1979a). In atrioventricular defects (Fig. 9) the entire mitral annulus or the mitral component of the common orifice is abnormally positioned relative to the area of mitral/aortic continuity so that instead of 'looking' downwards, leftwards, and anteriorly, it 'looks' more or less directly leftwards. The region of the mitral annulus that is most abnormal is the septal attachment, but the whole annulus is displaced relative to the aortic valve. The apical displacement of the septal attachment corresponds to the deficiency of the interventricular septum noted in anatomical studies (Blieden *et al.,* 1974; Ebert and Goor, 1978) and is associated with reorientation of the tricuspid annulus or component. This is because apical displacement of the septal attachment of the tricuspid valve towards the apex rotates the tricuspid annulus clockwise as seen from above. Thus the plane of the annulus 'looks' more anteriorly, and the lateral free wall attachment may even move to the left.

The only difference from these appearances in the case of complete malformations is that the direct septal attachment disappears largely or completely, leaving a common annulus (Fig. 9).

Because the realigned mitral annulus 'looks' more or less directly leftward, the septal attachment and free wall attachment in ostium primum lie essentially one in front of the other. Thus *either* can produce the characteristic 'scooped-out' appearance of the right margin of the left ventricular cavity in the frontal plane (Fig. 1). As Table 2 indicates, in only just under half the patients with ostium primum could this appearance be attributed to the septal attachment. In the remainder, as in the patients with complete defects, the abnormal 'scooped-out' appearance of this region was the result of the free wall attachment. The anatomical appearance of the 'scooped-out' septal crest which characterises atrioventricular defects is extremely beguiling because it looks so like the angiocardiographic abnormality. This resemblance can be enhanced by photographing the specimen in a mirror, reversing the negative (Blieden *et al.,* 1974) or painting the septal crest with contrast medium (Tenckhoff and Stamm, 1973), but none of these techniques proves that the septal crest can be visualised angiocardiographically in complete atrioventricular defects. It has been suggested that, during diastole, the leaflets float forward to contact the septal crest, thereby trapping contrast medium between it and the leaflets, but this argument ignores the fact that during the preceding systole, contrast medium will have passed to both sides of the septum thus preventing the sharp contrast between non-opacified and opacified blood which is required to

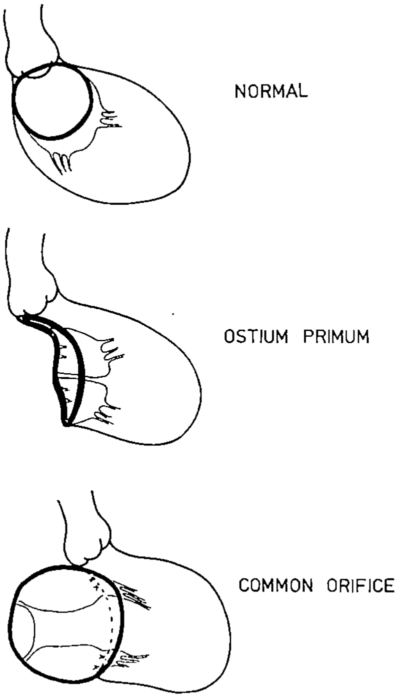

Fig. 9 *Diagram to demonstrate the anatomical cause of the radiographic appearances of the mitral valve or component in the frontal view of the left ventricular angiocardiogram in the normal and in partial and complete atrioventricular defects. In each diagram the entire annulus of the mitral valve or common valve is drawn in heavy black. The anterior mitral leaflet is also shown, but for clarity the posterior (mural) leaflet is not. In common atrioventricular orifice both anterior and posterior bridging leaflets are shown.*
Partial and complete defects have in common an abnormal position of the free wall attachment of the mitral annulus. They differ in that there is a direct septal attachment in ostium primum atrial septal defect which forms part of the annulus. In common atrioventricular orifice, the septal attachment is missing or deficient. There is therefore no reason why the crest of the septum (dotted) *should be visualised angiocardiographically except in so far as the chordal attachments to the septum are so tightly packed as to prevent passage of contrast medium through the interchordal spaces. Thus the mitral component of the free wall annulus, instead of passing onto the septum, is continuous with the tricuspid annulus component.*

demonstrate this apposition. The septal crest can, of course, be profiled, but then appears as a more or less permanent filling defect, disappearing only if it rotates out of profile. It is our contention that it is only possible to visualise the septal attachment during diastole when contrast medium is *not* free to cross from one side of the septum to the other during systole. This is the situation in ostium primum, and could only occur in complete defects if the leaflets were attached by short, densely packed chordae tendineae to the septal crest, in other words when there was virtually no ventricular component of the defect. A 'septal attachment' was visualised in two patients in whom the left and right anterior leaflets in a complete defect were attached to the septum but, as has been explained, these were seen on film changer exposures, not on cine angiograms, and were probably the result of passage of non-opacified blood through interchordal spaces.

By filming in oblique projections, the possibility of confusing the septal and free wall attachments of the mitral valve is eliminated, since they no longer overlap. This is one reason why Brandt's expositions of the radiographic appearances (Brandt *et al.*, 1972; Brandt, 1973) are models of clarity. Our own results endorse entirely Brandt's advocacy of the left anterior oblique projection for all varieties of antrioventricular defects, and further provide the clue to its superiority, which is that a common orifice is much more likely to be identified in diastole in the oblique projection than in the frontal and lateral projections. In contrast with Brandt, we have found the right anterior oblique projection helpful only in that it separates atria from ventricles, and therefore allows more certain identification of immediate right ventricular outflow tract (as opposed to right atrial) opacification after injection into the left ventricle. Adding craniocaudal tilt to the left anterior obliquity is of benefit in that it prevents foreshortening of an already deficient trabecular septum, thereby increasing the possibility of detecting additional ventricular septal defects. Indeed in some cases the combination of foreshortening and trabecular septal deficiency was so extreme that the diagnosis of univentricular heart was entertained until craniocaudal tilt was employed. On the other hand, in our experience, adding craniocaudal tilt to a left anterior oblique projection impairs visualisation of the atrioventricular valves, since they become foreshortened.

As predicted from the fundamental anatomy, right ventricular angiocardiography has proved to show abnormalities of the tricuspid valve or component in a number of patients. Where a common atrioventricular orifice was shown, the appearances were diagnostic and left ventricular angiocardiography served only to confirm what was already obvious. When the diagnosis of some type of atrioventricular defect was known from left ventricular angiocardiography, injection into the right ventricle frequently established the diagnosis of a common orifice by demonstrating passage of contrast medium above the anterior leaflet(s), or below the posterior bridging leaflet (Fig. 7A). It is therefore a valuable adjunct to left ventricular angiocardiography in cases where doubt may exist. Furthermore, it is useful in assessing the need for left ventriculography in apparently straightforward tetralogy of Fallot or double right ventricle. The right ventricular angiocardiograms may be diagnostic of the complete defect. Unless they clearly show separate tricuspid and mitral valves, one in each ventricle, left ventriculography should be carried out to exclude the presence of a common orifice, which greatly increases the operative risk (Sridaromont *et al.*, 1975). Left ventriculography is in any case useful for the purpose of excluding additional ventricular septal defects.

The results presented indicate that there is no universally applicable touchstone of either common orifice or ostium primum septal defect. A number of variables need to be considered, which is why discriminant function analysis has been applied. The results are instructive in so far as they indicate the relevance of each variable concerned. In particular, the right ventricular systolic pressure proved to be of considerable predictive value in addition to the angiocardiographic appearances. While it is true that some patients with ostium primum had a high right ventricular systolic pressure (Brandt *et al.*, 1972) and some with a common orifice had low right ventricular pressure, this predictor is widely applicable and no less accurate than, say, immediate filling of the right ventricular outflow tract from the left ventricle. For those disinclined to apply mathematical formulae to diagnosis, the results of the discriminant function equation may be roughly expressed as follows:

Whatever the right ventricular pressure, the diagnosis of common orifice is established if two of the following angiocardiographic signs are present, (a) evidence of a common orifice (b) systolic passage of contrast medium above the anterior leaflet(s), below the posterior leaflet, or across most of the atrioventricular annulus, (c) definite filling of the right ventricular outflow tract on the first systole after injection into the left ventricle. If the right ventricular pressure is 60 to 80 mmHg the diagnosis of a common orifice is established by (c) alone, or by two of (a), (b), or (probable c).

If the right ventricular pressure is 80 mmHg or above any one of the above angiocardiographic criteria establishes the diagnosis of a complete defect. If the criteria do not hold good, then the presumptive diagnosis is ostium primum atrial septal defect. Despite the large series of patients studied in whom there was independent confirmation of the diagnosis, no way was found of distinguishing the different varieties of leaflet attachment in complete defects. In particular, the appearance (Rastelli *et al.*, 1967) suggested as being typical of the 'free-floating' anterior leaflet, in which the anterior leaflet makes a sharp angle with the posterior line of attachment of the mitral valve, was frequently seen in all varieties of atrioventricular defects including ostium primum atrial septal defects (Fig. 2A).

The distinction between common orifice and ostium primum on the basis of the presence or absence of leaflet continuity over the crest of the septum has the great merit of leading to an unequivocal classification. However, it should be noted that this is not what is shown angiocardiographically. By angiocardiography one can hope to detect whether or not there is firm fusion of the leaflets to the crest of the septum. The method works because there is rarely continuity between anterior and posterior leaflets unless they are fused to the crest of the ventricular septum.

It is therefore to be expected that transitional forms of the defect, in which there is leaflet continuity but also a ventricular component, would be diagnosed as common atrioventricular orifice on angiocardiography.

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Comparison of haemodynamic effects of oral hydralazine and prazosin hydrochloride in patients with chronic congestive heart failure[1]

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SUMMARY The comparative haemodynamic effects of oral prazosin hydrochloride and hydralazine were evaluated in 11 patients with chronic congestive heart failure.

The maximum total dose of prazosin received by an individual varied up to 25 mg. Ten patients received a maximum of 75 mg and one received 50 mg of hydralazine at six-hour intervals. There was no significant change in heart rate with either drug. Decrease in mean arterial and left ventricular filling pressures were modest and similar with both agents. With prazosin, the average cardiac index increased 20 per cent and systemic vascular resistance decreased 20 per cent. By contrast, hydralazine increased cardiac index by 58 per cent and decreased systemic vascular resistance by 40 per cent. The increase in stroke work and stroke volume indices was significantly greater with hydralazine than with prazosin.

These findings suggest that in some patients with severe chronic congestive heart failure, improvement in left ventricular performance may be greater with hydralazine than with prazosin.

Vasodilator therapy is effective in some patients with chronic heart failure. Intravenous vasodilators can improve the haemodynamic and clinical status of patients in hospital with severe heart failure (Majid *et al.*, 1971; Guiha *et al.*, 1974; Chatterjee *et al.*, 1976a; Kovick *et al.*, 1976; Chatterjee and Parmley, 1977). Several nonparenteral vasodilators have also been investigated for long-term use in patients with chronic heart failure (Gold *et al.*, 1972; Franciosa *et al.*, 1974b; Gray *et al.*, 1975; Chatterjee *et al.*, 1976b; Kovick *et al.*, 1976; Mantle *et al.*, 1976; Taylor *et al.*, 1976). With accumulated experience, it is apparent that though most vasodilators produce qualitatively similar haemodynamic effects, the magnitude of the responses may differ significantly. Recently, the haemodynamic effects of two vasodilators, hydralazine and prazosin, have been investigated in different groups of patients with chronic congestive heart failure and beneficial responses to both drugs have been reported (Chatterjee *et al.*, 1976b; Franciosa *et al.*, 1977; Miller *et al.*, 1977; Awan *et al.*, 1977). However, no information about the comparative haemodynamic effects of these drugs in the same group of patients is available. The purpose of this study was to compare the haemodynamic effects of oral hydralazine and prazosin in the same patients with severe chronic congestive heart failure.

Methods

PATIENTS

The comparative effects of prazosin and hydralazine were investigated in 11 patients with chronic congestive heart failure. There were seven women and four men with an age range of 27 to 76 years. The aetiology of heart failure was ischaemic heart disease in seven patients, and cardiomyopathy of unknown cause in the other four. In two patients, there was a history of hypertension, though no patient was hypertensive at the time of the study. One patient had significant mitral regurgitation on the ventriculogram, in addition to poor left ventricular function, but in the other patients there was no clinical evidence of significant mitral regurgitation. All patients had clinical and radiological evidence of cardiomegaly, poor left ventricular function,

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pulmonary hypertension, and signs and symptoms of systemic and pulmonary venous congestion. Seven patients were in class IV of the New York Heart Association classification, four in class III.

The duration of heart failure ranged from seven months to five years. All patients were being treated with digitalis and diuretics. Serum digoxin levels at the time of the study ranged from 1·0 to 3·7 nmol/l (0·8 to 2·9 ng/ml). The diuretic and digoxin were continued throughout the study period. Three patients were in atrial fibrillation with a controlled ventricular response, while the remaining eight patients were in sinus rhythm at the time of the study.

HAEMODYNAMIC MEASUREMENTS

Pulmonary artery (PAP), pulmonary artery wedge (PAW), and right atrial (RAP) pressures were measured with the use of a triple lumen, balloon-tip flotation catheter (Forrester *et al.,* 1972). Pulmonary artery diastolic pressure was used as a measure of left ventricular filling pressure in one patient in whom a wedge pressure record could not be obtained. Mid-chest level was used as the reference point of the measurement of intracardiac pressures. Cardiac outputs were determined in triplicate by the thermodilution technique (Forrester *et al.,* 1972). The variability of triplicate cardiac output measurements was less than 10 per cent. Arterial mean pressure was measured by inserting a 20 gauge arterial cannula into the radial artery. In three patients with atrial fibrillation, arterial pressure was determined by averaging several consecutive beats. Derived haemodynamic indices were calculated as follows:

Cardiac index (CI) (l/min per m^2) = cardiac output/body surface area;

Stroke volume index (SVI) (ml per m^2) = CI/heart rate;

Stroke work index (SWI) (g m per m^2) = (LV mean systolic—PAW mean pressure) $\times$ SVI $\times$ 0·0136;

Systemic arterial mean pressure (MAP) (mmHg)

$$= \text{diastolic pressure} + \frac{\text{systolic–diastolic}}{3};$$

Systemic vascular resistance (SVR) (dynes s cm^{-5})

$$= \frac{\text{MAP} - \text{mean RA pressure}}{\text{cardiac output}} \times 80;$$

Pulmonary vascular resistance (PVR) (dynes s cm^{-5})

$$= \frac{\text{PA mean} - \text{PAW mean pressure}}{\text{cardiac output}} \times 80$$

DRUG ADMINISTRATION

After initial control haemodynamic measurements had been made, prazosin was administered first in eight patients, followed by oral hydralazine. In three patients, oral hydralazine was administered first, and then oral prazosin.

The initial oral dose of prazosin was 40 to 50 μg per kg (2 mg in four patients and 3 mg in seven patients), comparable with the dose selected by previous investigators (Awan *et al.,* 1977). Haemodynamic measurements were repeated hourly. Prazosin was then given in doses increasing by 1 mg at three-hour intervals, until a 5 mg dose was administered. Nine patients received two additional 5 mg doses at eight hour intervals.

The initial oral dose of hydralazine was 50 mg which was increased six hours later to 75 mg in 10 of 11 patients; in one patient there was a large increase in cardiac output with 50 mg hydralazine, and the dose was not increased. Haemodynamic measurements were repeated hourly. Oral hydralazine was then given at six-hour intervals up to 36 hours, with frequent haemodynamic measurements.

After determination of the haemodynamic response to the first drug administered (prazosin or hydralazine), the haemodynamic variables were allowed to return to control levels over 12 to 24 hours. Haemodynamic measurements were repeated to ensure return to control levels before the administration of the second drug; those obtained before administration of this drug served as control. Haemodynamic measurements made at the time of maximum effect of the drug on cardiac index were recorded at each dose level for both drugs and compared.

Statistical analyses of the data used a two-way analysis of variance, without replication and a mixed effects model. Data were expressed as the mean ±standard error of the mean (SEM).

Results

The control haemodynamic data before the administration of prazosin (C1) or hydralazine (C2), irrespective of the order of their administration, were remarkably similar (Table). The average cardiac index was almost the same and there were only minor differences in other haemodynamic measurements, none of which were statistically significant.

HAEMODYNAMIC EFFECTS OF ORAL PRAZOSIN

The maximum haemodynamic response was defined in terms of increase in cardiac output and was usually observed one to two hours after the first

Table *Haemodynamic effects (mean ± SEM) of oral prazosin and hydralazine in patients with chronic congestive heart failure*

	HR *(beats/min)*	*MAP* *(mmHg)*	*MPAP* *(mmHg)*	*LVFP* *(mmHg)*	*RAP* *(mmHg)*	*CI* *(l/min per m²)*	*SVI* *(ml per m²)*	*SWI* *(g m per m²)*	*SVR* *(dynes s cm⁻⁵)*	*PVR* *(dynes s cm⁻⁵)*
C(1)	86 ± 7	87 ± 3	36 ± 2	24 ± 1	12 ± 1	2·0 ± 0·1	26 ± 2	22 ± 3	1776 ± 85	285 ± 40
P 3 mg	83 ± 4	80 ± 2	28 ± 2	19 ± 2	10 ± 2	2·5 ± 0·2	31 ± 2	26 ± 3	1373 ± 82	194 ± 41
P 4 mg	85 ± 5	84 ± 3	28 ± 2	19 ± 2	10 ± 1	2·4 ± 0·2	29 ± 2	25 ± 3	1631 ± 167	222 ± 31
P 5 mg	79 ± 3	79 ± 3	28 ± 3	19 ± 2	8 ± 1	2·5 ± 0·2	30 ± 3	25 ± 3	1410 ± 118	186 ± 29
C(2)	87 ± 7	87 ± 3	35 ± 2	24 ± 1	12 ± 1	2·0 ± 0·1	25 ± 2	22 ± 2	1760 ± 86	270 ± 45
HD 50 mg	86 ± 7	82 ± 3	30 ± 3	21 ± 2	11 ± 1	2·5 ± 0·1	32 ± 3	27 ± 3	1400 ± 111	214 ± 31
HD 75 mg	89 ± 6	79 ± 2	30 ± 2	20 ± 2	11 ± 2	3·3 ± 0·2	38 ± 3	30 ± 2	1045 ± 60	203 ± 25
HD 75 mg vs P 5 mg	—	—	—	—	*	‡	‡	*	†	—
C(1) vs P 5 mg	—	*	†	**	**	‡	**	—	***	*
P3 vs 4 mg vs 5 mg	—	—	—	—	—	—	—	—	—	—
C(2) vs HD 50 mg	—	***	**	*	—	†	***	*	‡	*
HD 50 mg vs 75 mg	—	**	—	—	—	†	***	—	‡	—

*$P < 0·05$; **$P < 0·025$; ***$P < 0·01$; †$P < 0·005$; ‡$P < 0·001$.
C(1): control before prazosin; C(2): control before hydralazine; CI: cardiac index; HD: hydralazine; HR: heart rate; LVFP: left ventricular filling pressure; MAP: systemic arterial mean pressure; MPAP: pulmonary artery mean pressure; P: prazosin; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SVI: stroke volume index; SWI: stroke work index; SVR: systemic vascular resistance.

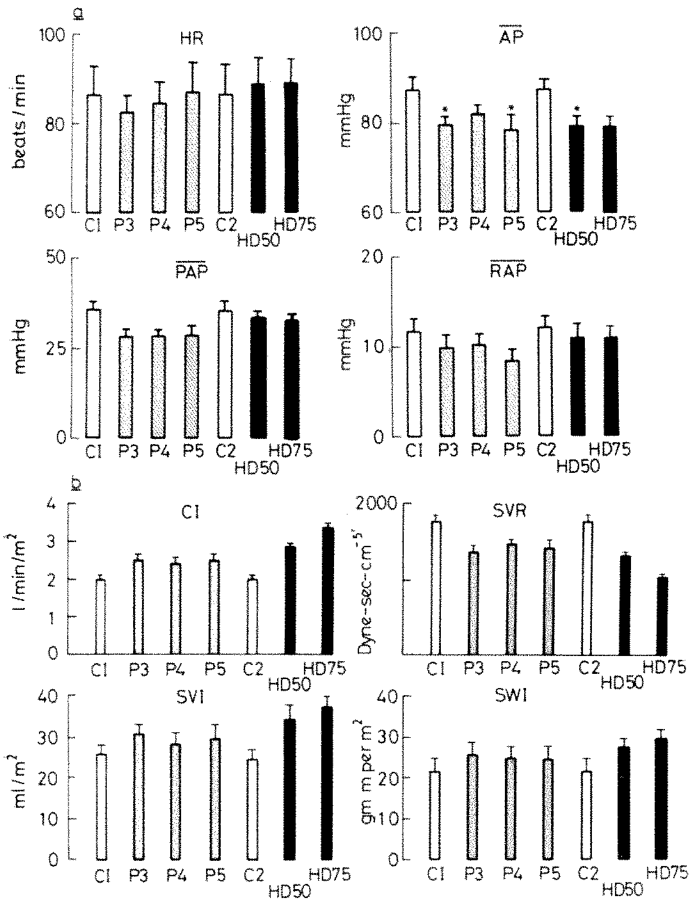

Fig. 1 *Effects of oral prazosin (3, 4, and 5 mg) and oral hydralazine (50 and 75 mg) on heart rate (HR), systemic arterial ($\overline{AP}$), pulmonary arterial ($\overline{PAP}$), and right atrial ($\overline{RAP}$) mean pressures and on cardiac index (CI), stroke volume index (SVI), stroke work index (SWI), and systemic vascular resistance (SVR). Control values before prazosin (C1) and before hydralazine (C2) were not different. Compared with controls, changes in systemic and pulmonary arterial pressures were similar with the two drugs. However, the mean increase in cardiac index and the decrease in systemic vascular resistance with hydralazine were significantly greater than with prazosin. Haemodynamic changes after 3, 4, or 5 mg prazosin were of similar magnitude.*
P3, P4, P5 = prazosin 3, 4, and 5 mg; HD50, HD75 = hydralazine, 50 and 75 mg.

dose. However, at the time of maximal increase in cardiac output, other haemodynamic changes were also observed. The haemodynamic changes after 3, 4, and 5 mg doses of oral prazosin are summarised in the Table and in Fig 1a and 1b. Heart rate did not change significantly in any patient during prazosin treatment. There were slight but statistically significant decreases in pulmonary artery wedge, right atrial, mean pulmonary arterial, and mean systemic arterial pressures. There was a significant increase in cardiac index along with a decrease in systemic vascular resistance. Stroke volume and stroke work indices increased in most patients, though the increase in stroke work index was not statistically significant. An increase in stroke volume index, accompanying a decrease in pulmonary artery wedge pressure, suggested improved left ventricular performance. Haemodynamic changes were usually observed after the initial dose of 2 to 3 mg oral prazosin. There were no further changes when the dose was increased to 4 or 5 mg. In an attempt to increase the response, two patients received a 20 mg dose of prazosin without further increment in cardiac output or reduction in systemic vascular resistance.

HAEMODYNAMIC EFFECTS OF ORAL HYDRALAZINE

In the same patients, the maximum haemodynamic response in terms of increase in cardiac output was also observed at one to two hours after administration of oral hydralazine. Haemodynamic changes after hydralazine in doses of 50 mg and 75 mg are summarised in the Table and in Fig. 1a and 1b. After 75 mg hydralazine, there was no significant change in heart rate. There were slight, but statistically significant falls in pulmonary and systemic arterial and pulmonary artery wedge pressures. Right atrial pressure was unchanged. A small decrease in pulmonary vascular resistance was noted. There was a large increase in cardiac index (average 58%) and a significant decrease in systemic vascular resistance. Stroke volume and stroke work indices increased greatly in most patients. Cardiac index, systemic vascular resistance, and stroke volume index after 50 mg hydralazine were intermediate, being significantly different from control measurements, though the changes were less than those seen at the 75 mg dose level. During continued administration of 75 mg hydralazine, the haemodynamic changes were persistent.

COMPARISON BETWEEN HAEMODYNAMIC EFFECTS OF PRAZOSIN AND HYDRALAZINE (FIG. 2)

There was a significant difference between the maximal effects of prazosin (5 mg) and hydralazine (75 mg) on cardiac output and systemic vascular resistance. The average increase in cardiac output during prazosin treatment was 25 per cent. By contrast, hydralazine increased cardiac output by 58 per cent ($P < 0{\cdot}001$). The decrease in calculated systemic vascular resistance during prazosin treatment (–20%) was significantly less than that produced by hydralazine (–40%). The increase in stroke work and stroke volume indices was also significantly greater with hydralazine than with prazosin. The small decreases in pulmonary artery wedge pressure with prazosin (–21%) and with hydralazine (–20%) were, however, similar. There was no significant change in heart rate with either drug. The decrease in systemic arterial mean pressure was small (–8 mmHg) with both drugs. Postural hypotension and other untoward side effects did not occur with either drug during the period of administration.

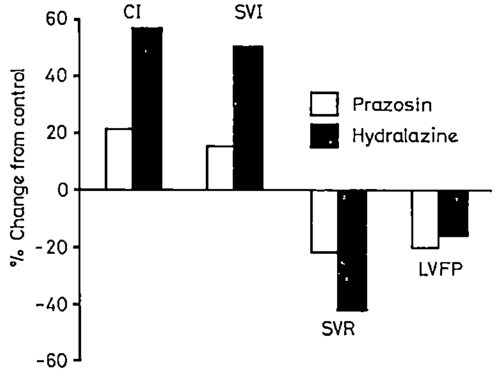

Fig. 2 *Comparison between the haemodynamic effects of prazosin (5 mg) and hydralazine (75 mg) in patients with chronic heart failure. The magnitude of the decrease in left ventricular filling pressure (LVFP) was similar with both drugs. However, the increase in cardiac index (CI) and stroke volume index (SVI) and the decrease in systemic vascular resistance (SVR) were greater with hydralazine than with prazosin. The differences between the changes in CI, SVI, and SVR were statistically significant, whereas the difference between the changes in LVFP were not.*

On the other hand, there were no significant differences between the haemodynamic changes after prazosin and those after the lower dose of hydralazine (50 mg).

Discussion

Beneficial haemodynamic effects of various nonparenteral vasodilator drugs in patients with chronic congestive heart failure have been documented in previous investigations. The most widely used nonparenteral vasodilators until recently have been the nitrates which, with adequate doses, decrease pulmonary and systemic venous pressures significantly in most patients (Franciosa *et al.*, 1974b; Kovick *et al.*, 1976). Though in some patients cardiac output increases, in the majority there is little or no change with the use of nitrates (Mantle *et al.*, 1976; Chatterjee and Parmley, 1977). Since the major haemodynamic objectives of treatment of heart failure are to improve cardiac output and decrease systemic and pulmonary venous pressures, the search continues for more effective vasodilator drugs which can be used either alone or in combination (Awan *et al.*, 1977; Parmley and Chatterjee, 1976). Recently, the haemodynamic effects of the two antihypertensive agents, hydralazine (Chatterjee *et al.*, 1976b; Franciosa *et al.*, 1977) and prazosin (Awan *et al.*, 1977; Miller *et al.*, 1977) have been investigated in patients with chronic congestive heart failure and a beneficial response to both drugs has been documented.

The present study confirms the beneficial haemodynamic effects of both vasodilator agents in patients with chronic congestive heart failure. Thus, with prazosin, there was usually an increase in cardiac output together with some decrease in pulmonary artery wedge pressure, suggesting improved left ventricular performance. However, there appears to be a significant difference between the haemodynamic response to prazosin observed in the present study and that reported by Miller *et al.* (1977) and by Awan *et al.* (1977) who observed a distinct decrease in pulmonary artery wedge pressure (–45%), as compared with the present study (–21%). The average increase in cardiac output in the present study (+23%) was also appreciably less than that (+48%) reported by Awan *et al.* (1977). These discrepancies were not the result of inadequate doses of prazosin; the cumulative dose in our study ranged up to 25 mg, which was more than in previous studies. Furthermore, the haemodynamic response was no better with increasing doses of prazosin. In our patients, the beneficial haemodynamic response was usually observed with the initial 3 mg dose of oral prazosin. There was no further significant change when the dose was increased (Fig. 1a and b). Furthermore, preliminary investigations in our laboratory suggest a poor correlation between the haemodynamic effects of prazosin and its blood level (Arnold *et al.*, 1979).

Differences in patient population may explain some of the differences observed in the response to prazosin. In the present study, almost all of our patients with chronic congestive heart failure were normotensive at the time of the investigation and the decrease in systemic arterial pressure was only slight, even with larger doses of prazosin. In the patients investigated by Miller *et al.* (1977) and Awan *et al.* (1977), the mean arterial pressure was considerably higher and the decrease in arterial pressure was also considerably greater. Since there is a relation between changes in arterial pressure and changes in pulmonary artery wedge pressure (Franciosa *et al.*, 1974a), a large fall in arterial pressure will be associated with a more pronounced fall in pulmonary artery wedge pressure, as was observed in the patients studied by Miller *et al.* (1977) and Awan *et al.* (1977). In our normotensive patients, the decrease in arterial pressure with prazosin was less, as was the decrease in pulmonary artery wedge pressure.

These results confirm our previous experience with oral hydralazine (Chatterjee *et al.*, 1976b). There was a significant increase in cardiac output associated with a decrease in calculated systemic vascular resistance. Additionally, the haemodynamic effects were greater when the dose of hydralazine was raised from 50 mg to 75 mg. There was only a slight decrease in systemic arterial pressure without any significant change in heart rate. In many patients, there was some decrease in pulmonary artery wedge pressure after oral hydralazine, but this decrease, however, was relatively small. Though in our previous study a consistent decrease in pulmonary artery wedge pressure was not observed (Chatterjee *et al.*, 1976b), other investigators have reported a fall in wedge pressure after oral administration of hydralazine in patients with chronic heart failure (Franciosa *et al.*, 1977). The difference in the degree of systolic unloading of the left ventricle in different patient populations with varying severity of depression of cardiac function may account, to some extent, for the variations in the haemodynamic findings. With more severe depression of cardiac function, a better 'unloading' effect is expected. In the present study, almost all patients had severe heart disease and advanced left ventricular failure.

This study was designed to investigate the comparative haemodynamic effects of prazosin and hydralazine in the same patients with chronic congestive heart failure. The doses of these drugs were chosen on the basis of those shown to produce beneficial haemodynamic responses in different patient populations (Chatterjee *et al.*, 1976b); Awan *et al.*, 1977). Comparison of haemodynamic effects of hydralazine and prazosin in the same patients indicates that, in the prescribed doses, hydralazine produced greater haemodynamic effects than prazosin. The average increase in cardiac output with hydralazine was +58 per cent compared with

+25 per cent increase with prazosin, a highly significant difference (P < 0·001). The increase in stroke volume and stroke work indices was also significantly greater with hydralazine. The decrease in pulmonary artery wedge pressure was similar with hydralazine and prazosin. These findings indicate that, though both drugs improved left ventricular performance, improvement with hydralazine was greater than with prazosin (Fig. 3).

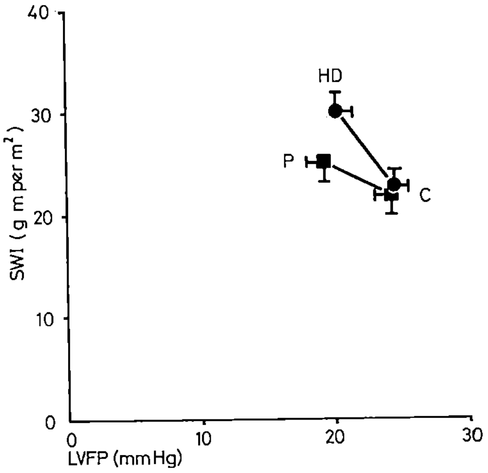

Fig. 3 *The influence of oral hydralazine (75 mg) (HD) and oral prazosin (5 mg) (P) on left ventricular function in patients with chronic heart failure. There was a greater increase in stroke work index (SWI) with hydralazine than with prazosin. With prazosin left ventricular filling pressure (LVFP) decreased to 19±2 from control (24±1 mmHg). With hydralazine, LVFP decreased to 20±2 mmHg from control (24±1 mmHg). The difference between the decreases in LVFP with prazosin and hydralazine was not statistically significant.*

Of the 11 patients in this study, eight received prazosin initially; though hydralazine was not given to these patients until the haemodynamic measurements had returned to control levels, the possibility exists that the altered circulatory state induced by prazosin was still present when hydralazine was administered, accounting for a greater increase in cardiac output with hydralazine. However, in three patients who received hydralazine first, a similar difference in the haemodynamic response between hydralazine and prazosin was observed. Furthermore, in previous studies, in which hydralazine was not preceded by prazosin, a similar haemodynamic response was observed (Chatterjee *et al.*, 1976b). It seems unlikely, therefore, that a better haemodynamic response to hydralazine can be explained by a possible alteration in the circulatory state induced by previously administered prazosin.

In conclusion, the present study suggests that hydralazine may be more effective than prazosin in improving left ventricular performance in some patients with severe chronic congestive heart failure. However, the potential complications of long-term hydralazine treatment may be considerable. The lupus syndrome, pyridoxine deficiency polyneuropathy, fluid retention, and weight gain may preclude the use of hydralazine in some patients (Perry, 1973). In such circumstances, prazosin may be a reasonable alternative drug to consider.

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Comparison of haemodynamic effects of oral prazosin, oral hydralazine, and intravenous nitroprusside in same patients with chronic heart failure[1]

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SUMMARY The haemodynamic effects of oral prazosin and hydralazine were evaluated in patients with refractory heart failure and compared with those of intravenous nitroprusside in the same patients. Both oral agents were well tolerated and appeared to have beneficial haemodynamic effects. Prazosin and hydralazine produced similar increases in cardiac output associated with a similar decrease in systemic vascular resistance. Prazosin resulted in a more significant decline in left ventricular filling pressure and pulmonary vascular resistance than did hydralazine. Haemodynamic alterations induced by prazosin were similar to those induced by nitroprusside, which suggests a relatively balanced reduction of preload and afterload. With hydralazine, the increase in cardiac output without change in left ventricular filling pressure or pulmonary vascular resistance suggests minimal effect on preload but significant reduction in afterload.

A decrease in left ventricular afterload in patients with heart failure improves left ventricular function by increasing stroke volume and decreasing left ventricular filling pressure (Franciosa *et al.*, 1972; Chatterjee *et al.*, 1973a; Guiha *et al.*, 1974). This has been shown in heart failure associated with a variety of pathological states, such as coronary heart disease (Franciosa *et al.*, 1972; Chatterjee *et al.*, 1973a), mitral and aortic regurgitation (Chatterjee *et al.*, 1973b; Bolen and Alderman, 1976), and hypertensive heart disease (Majid *et al.*, 1971). Reduction of preload lowers left ventricular filling pressure but does not consistently result in increased stroke volume (Franciosa *et al.*, 1974; Mantle *et al.*, 1976).

Intravenously administered nitroprusside produces a rapid increase in cardiac output and fall in left ventricular filling pressure in certain patients with heart failure as a result of afterload and preload reduction. Because nitroprusside must be given parenterally, its usefulness is limited to patients in hospital. Thus, it would be clinically useful if oral agents with a similar mode of action were available to increase stroke volume and decrease pulmonary congestion in patients with heart failure. In ambulant patients with heart failure, both hydralazine (Chatterjee *et al.*, 1976b; Franciosa *et al.*, 1977; Mehta *et al.*, 1978b) and prazosin (Awan *et al.*, 1977; Mehta *et al.*, 1978a) have shown promise in preliminary studies. However, in individual patients with heart failure, the haemodynamic response to vasodilators can vary (Chatterjee and Parmley, 1977). We therefore compared the haemodynamic and clinical effects of various vasodilator agents in the same patients. This study was designed so that the effects of two oral vasodilator agents, hydralazine and prazosin, could be evaluated, and the effects of these compared with those induced by intravenous nitroprusside in the same patients.

Patients and methods

The subjects were 11 male patients, aged 37 to 65 years, with symptoms and signs of clinical heart failure (New York Heart Association class III or IV) despite treatment with digitalis, diuretics, and salt restriction. The duration of heart failure ranged from 3 to 7 years before study. In all, heart failure was the result of coronary heart disease, documented by history, electrocardiogram, and previous coronary angiography. None complained of angina pectoris at the time of study. Each of these patients

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had areas of abnormal left ventricular wall motion observed during left ventriculography, and all had an enlarged heart. A left ventricular diastolic gallop was heard in seven patients. Basal râles were present in seven. All patients were in sinus rhythm, though three had occasional atrial or ventricular ectopic beats. These clinical observations were made before haemodynamic study.

HAEMODYNAMIC STUDIES

The procedure and drugs to be used were explained to the patients, and their informed consent was given. Investigations were performed in a special study room of the cardiac care unit, so that haemodynamic variables could be monitored and recorded for the duration of study. Digitalis was continued, but diuretic agents (hydrochlorothiazide 50 mg daily in six patients and frusemide 40 mg daily in the other five) and nitrates were withheld for two days before study. These agents were discontinued so that haemodynamic variables were affected primarily by the study drugs rather than the acute effects of diuretics and nitrates. The patients were kept at bed-rest for at least eight hours before and throughout the study period. A triple lumen flow-directed catheter was advanced to the pulmonary artery, and a 'teflon' catheter was introduced percutaneously into the radial artery to measure systemic blood pressure. Systemic and pulmonary arterial pressures and pulmonary artery wedge pressure were recorded on a VR-6 recorder (Electronics for Medicine, White Plains, NY) with Statham P23Ia strain gauge transducers. Systolic and diastolic pressures were averaged from at least 10 beats measured over two respiratory cycles. Mean pressures were obtained by electronic filtration. The occluded pulmonary artery pressure recorded during balloon inflation was taken as pulmonary artery wedge pressure and agreed closely with pulmonary artery diastolic pressure in each patient; either of these measurements was used as an index of left ventricular filling pressure. All pressure measurements were recorded with reference to midchest zero with the patient supine. Heart rate was averaged from recordings of a standard electrocardiographic lead. Cardiac output was measured in triplicate by thermodilution (Ganz and Swan, 1972) and reported as the average of these three determinations.

The following calculations were made:

CI (l/min per m^2) $=$ CO/BSA

SV (ml/beat) $=$ CO/HR

SVI (ml/beat per m^2) $=$ SV/BSA

LVSWI (g m/m^2) $=$ SVI $\times (\overline{\text{Ao}} - \text{LVFP}) \times 0{\cdot}0136$

SVR (dynes s cm^{-5}) $= \overline{\text{Ao}} \times 80/\text{CO}$

PVR (dynes s cm^{-5}) $= (\overline{\text{PA}} - \text{LVFP}) \times 80/\text{CO}$

Index of myocardial oxygen demand $=$ SAP $\times$ HR.

(Abbreviations: CI, cardiac index: CO, cardiac output; BSA, body surface area; SV, stroke volume; HR, heart rate; LVSWI, left ventricular stroke work index; SVI, stroke volume index; $\overline{\text{Ao}}$, arterial mean pressure; LVFP, left ventricular filling pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; $\overline{\text{PA}}$, pulmonary arterial mean pressure; and SAP, arterial systolic pressure.

Patients were evaluated clinically during the control period and hourly during drug administration.

STUDY PROCEDURE

General design

Before each of the three drug study periods, control haemodynamic recordings were obtained during a haemodynamically stable interval when pressures, cardiac output, and heart rate were unchanged (±10%) from initial baseline values over 30 minutes with repeated measurements. Haemodynamic recordings were then repeated during drug administration. These recordings included heart rate, systemic and pulmonary artery pressures, and cardiac output.

Nitroprusside administration

Nitroprusside was given by an infusion pump into a peripheral vein starting at 10 μg/min. The infusion rate was increased by 10 μg/min increments every 10 minutes until either left ventricular filling pressure fell to 15 mmHg or less, cardiac output increased by 50 per cent or more, or systolic arterial pressure fell by 20 mmHg or more from the control value or to 100 mmHg. Haemodynamic measurements, outlined above, were made at each increment in dose. Nitroprusside infusion was then discontinued.

Prazosin administration

After re-establishment of a stable control interval, as noted above, 4 mg prazosin was administered orally. Haemodynamic measurements were made every hour for eight hours.

Hydralazine administration

After haemodynamically stable values were re-established, similar to those before nitroprusside or prazosin (Table 1), 100 mg hydralazine was administered orally. Haemodynamic measurements were made hourly for eight hours.

The order of the administration of the three vasodilators is shown in Table 1. Prazosin and nitroprusside were given in random order, but hydralazine was given to only seven patients who agreed to participate in the final phase of the study.

Table 1 *Order of drug administration*

Case no.	*Drug study period*		
	I	*II*	*III*
1	NP	P	H
2	NP	P	H
3	NP	P	—
4	NP	P	—
5	NP	P	—
6	P	NP	H
7	P	NP	H
8	P	NP	H
9	P	NP	H
10	P	NP	H
11	P	NP	—

Abbreviations: NP, intravenous nitroprusside; P, oral prazosin (4 mg); H, oral hydralazine (100 mg).

Data analysis

Mean values and standard error of the mean were calculated during each control and treatment period. Mean values in the control state and at the peak effect of each drug were compared. To test for the interaction, the repeated measures analysis of variance model was used. For the purpose of comparison of three drugs, in the seven patients who received all three drugs, Duncan's multiple comparison test was employed (Winer, 1971). A P value less than 0·05 was considered statistically significant.

Results

CONTROL STATE

All haemodynamic variables were comparable in the control state before administration of the three drugs.

PEAK EFFECT

Maximal change in haemodynamic variables observed with nitroprusside, prazosin, and hydralazine are presented in Table 2.

The effects of nitroprusside were apparent soon after infusion was started and abated when the infusion was discontinued. The change in haemodynamic variables occurred half to one hour after prazosin administration and lasted for six hours. In all patients given hydralazine, the alteration in haemodynamics induced by nitroprusside or prazosin had abated and haemodynamics returned to control levels (Table 2). The interval between prazosin and hydralazine administration varied from 10 to 18 hours (mean 12 hours). The effects of

Table 2 *Haemodynamic effects of nitroprusside, prazosin, and hydralazine in heart failure patients*

Case no.		*HR (beats/min)*			*MAP (mmHg)*			*MPA (mmHg)*			*LVFP (mmHg)*			*CI (l/min per m²)*		
		N	*PR*	*H*	*N*	*PR*	*H*	*N*	*PR*	*H*	*N*	*PR*	*H*	*N*	*PR*	*H*
1	C	88	79	76	95	105	79	39	39	35	32	27	27	1·14	1·15	1·38
	P	72	70	86	98	88	91	26	28	31	18	16	23	1·89	1·88	1·38
2	C	80	80	80	85	85	85	29	29	29	21	21	21	1·98	1·99	1·93
	P	80	88	80	78	83	88	22	26	28	16	17	20	2·38	2·39	3·13
3	C	74	79	89	120	138	115	38	39	38	24	28	24	2·10	2·14	2·59
	P	85	96	91	97	102	90	18	17	26	12	14	22	2·71	2·69	3·90
4	C	96	98	90	88	84	82	32	35	29	25	25	24	2·02	2·02	2·19
	P	82	90	84	71	80	72	14	26	29	11	16	19	2·42	2·25	2·94
5	C	108	105	105	73	74	76	35	37	35	30	24	30	1·69	1·92	1·70
	P	106	99	96	70	69	78	29	32	35	25	23	30	2·66	2·31	2·53
6	C	78	80	72	85	79	80	39	42	36	27	32	29	1·89	1·86	1·28
	P	68	68	75	70	68	77	20	34	37	12	22	28	2·69	1·89	1·77
7	C	89	77	88	78	87	78	33	39	34	26	30	26	2·14	1·68	2·10
	P	80	82	84	70	78	80	20	32	30	10	19	21	2·92	2·70	3·48
8	C	58	58	—	72	80	—	46	39	—	29	24	—	2·99	2·35	—
	P	56	56	—	62	66	—	23	26	—	14	17	—	3·16	2·67	—
9	C	87	83	—	103	99	—	53	51	—	38	34	—	2·92	2·58	—
	P	97	77	—	77	73	—	30	38	—	19	21	—	3·71	3·54	—
10	C	100	92	—	105	122	—	45	54	—	40	39	—	1·49	1·54	—
	P	84	80	—	93	96	—	37	28	—	28	19	—	3·03	1·84	—
11	C	70	70	—	100	100	—	47	48	—	23	25	—	1·97	2·14	—
	P	70	70	—	87	94	—	30	38	—	14	20	—	2·89	2·39	—
Mean (7 patients, 1–7)																
±SEM	C	88	85	85	89	93	88	36	37	34	26	27	26	1·85	1·82	1·88
		4	4	3	6	8	5	1	2	1	1	1	1	0·13	0·12	0·18
	P	82	85	85	79**	81*	82	21*	28*	31	15*	18*	23**	2·52*	2·30*	2·73*
		5	5	3	5	4	3	2	2	1	2	1	2	0·13	0·13	0·34
Mean (all 11 patients)																
±SEM	C	84	82	—	91	96	—	40	41	—	29	28	—	2·03	2·00	—
		·4	4	—	4	6	—	2	2	—	2	2	—	0·16	0·15	—
		80	80	—	79*	82*	—	24*	30*	—	16*	19*	—	2·77*	2·41*	—
		4	4	—	4	4	—	2	2	—	2	1	—	0·14	0·15	—

Abbreviations: N, IV nitroprusside; PR, prazosin; H, hydralazine; HR, heart rate; MAP, systemic arterial mean pressure; MPA, pulmonary artery mean pressure; LVFP, left ventricular filling pressure; CI, cardiac index; LVSWI, left ventricular stroke work index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; C, control; P, peak effect; *P < 0·01 (peak vs control).; **P < 0·02 (peak vs control).

hydralazine were observed at three hours and persisted for eight hours.

Nitroprusside and oral prazosin produced significant increases in cardiac index and left ventricular stroke work. Both agents decreased mean arterial, pulmonary arterial, and left ventricular filling pressures, and systemic and pulmonary vascular resistances. Heart rate was unchanged. Oral hydralazine administration significantly increased cardiac index and left ventricular stroke work, and decreased systemic vascular resistance and left ventricular filling pressure. Hydralazine did not affect heart rate, systemic and pulmonary arterial pressures, pulmonary vascular resistance, or systolic arterial pressure-heart rate product.

NITROPRUSSIDE VS PRAZOSIN

Comparison of the effects of these two vasodilator agents in all patients showed that they induced a similar increase in cardiac index (0·74±0·11 vs 0·47±0·09 l/min per m^2, NS) and a fall in left ventricular filling pressure (11±2 vs 10±2 mmHg, NS). The fall in resistance in the systemic (791±150 vs 640±165 dynes s cm^{-5}) and pulmonary vascular (98±29 vs 96±24 dynes s cm^{-5}) beds was comparable (NS), as was the decrease in heart rate (3±3 vs 2±3 beats/min), arterial mean (12±3 vs 14±3 mmHg), and pulmonary artery mean pressures (15±2 vs 11±2 mmHg, NS). The increase in left ventricular stroke work (8·61±2·10 vs 4·09±1·96 g m per m^2) was however more with nitroprusside than with prazosin ($P < 0·007$). Decrease in arterial systolic pressure-heart rate product (1450±250 vs 1254±309, NS) were also similar with both agents. Both drugs similarly affected the relation between left ventricular filling pressure and stroke work (Fig.).

LVSWI (g m per m^2)			*SVR (dynes s cm^{-5})*			*PVR (dynes s cm^{-5})*		
N	*PR*	*H*	*N*	*PR*	*H*	*N*	*PR*	*H*
11·10	15·44	17·29	3160	3462	2665	233	396	220
28·56	26·29	14·84	1966	1774	2500	160	242	220
21·54	21·65	20·99	1908	1898	1957	180	179	184
25·08	24·38	36·18	1456	1543	1249	112	167	113
37·05	40·52	36·01	2078	2344	1615	242	187	197
36·86	33·54	39·63	1301	1379	839	81	41	37
18·03	16·54	19·19	1958	1868	1682	156	222	103
24·08	21·76	25·23	1319	1598	1101	56	200	153
9·15	12·43	10·12	1899	1694	1965	130	297	129
15·36	14·60	17·20	1644	1869	1927	94	244	124
19·11	14·86	12·33	2194	2072	3049	310	262	419
31·20	17·39	15·73	1269	1755	2122	145	310	248
17·00	16·91	16·88	1389	1973	1414	125	204	145
29·78	26·42	33·24	913	1101	876	130	183	99
30·14	30·86	—	1030	1456	—	243	273	—
36·83	31·77	—	839	1058	—	122	144	—
29·67	27·48	—	1585	1726	—	231	296	—
30·17	32·51	—	932	927	—	133	216	—
13·17	18·90	—	2805	3153	—	134	388	—
31·89	24·09	—	1221	2076	—	118	195	—
29·47	31·18	—	2030	1869	—	487	430	—
40·99	34·36	—	1204	1573	—	221	301	—
19·00	19·77	18·98	2084	2187	2050	196	250	200
3·44	3·62	3·18	203	226	225	26	29	40
27·28*	23·48*	26·01*	1410*	1574*	1516*	111*	198*	142
2·55	2·38	3·93	125	100	250	14	32	27
21·40	22·43	—	2003	3138	—	225	285	—
2·72	2·67	—	179	188	—	32	26	—
30·07*	26·10*	—	1279*	1514*	—	125*	204*	—
2·12	1·97	—	100	110	—	13	23	—

NITROPRUSSIDE VS HYDRALAZINE

Cardiac index increased similarly (1·20±0·47 vs 0·85±0·19 l/min per m^2, NS) with nitroprusside and hydralazine in the same seven patients. However, left ventricular filling pressure declined more with nitroprusside (12±2 vs 3±1 mmHg, $P < 0·0005$). The fall in systemic vascular resistance was similar with nitroprusside and hydralazine (673±120 vs 533±122 dynes s cm^{-5}, NS). Pulmonary vascular resistance fell more (88±24 vs 58±31 dynes s cm^{-5}, $P < 0·01$) with nitroprusside. Though changes in heart rate and mean arterial pressure were not different, pulmonary artery mean pressure fell more with nitroprusside than with hydralazine (14±2 vs 3±2 mmHg, $P < 0·001$). Left ventricular stroke work increased to a similar degree (8·28±2·30 vs 5·67±2·01 g m per m^2, NS).

PRAZOSIN VS HYDRALAZINE

Comparison of the haemodynamic effects of the two oral agents in the same patients showed that cardiac

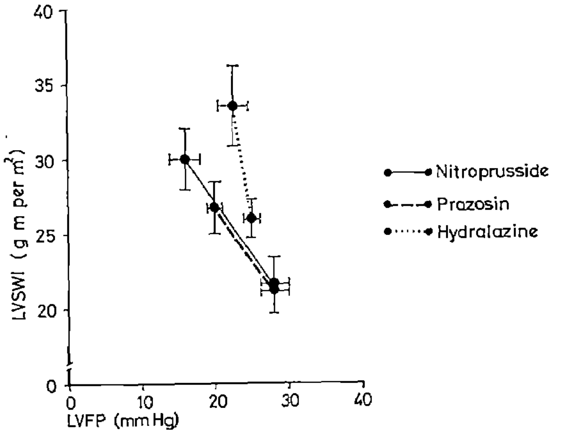

Fig. *Effect of intravenous nitroprusside, oral prazosin, and hydralazine on the relation between left ventricular filling pressure (LVFP) and left ventricular stroke work index (LVSWI) in patients with heart failure. Intravenous nitroprusside and prazosin have similar action on the LVFP LVSWI relation, whereas hydralazine increases LVSWI without affecting LVFP.*

index increased similarly (0·48 ±0·09 vs 0·85 ±0·19 l/min per m^2, NS) with prazosin and with hydralazine. However, left ventricular filling pressure fell more with prazosin than with hydralazine (8 ±2 vs 3 ±1 mmHg, $P < 0·005$). The fall in systemic vascular resistance (744 ±194 vs 533 ±122 dynes s cm^{-5}, NS) and pulmonary vascular resistance (46 ±25 vs 58 ±31 dynes s cm^{-5}, NS) was similar with the two drugs. Changes in heart rate and arterial mean pressure were not significantly different (NS). However, pulmonary arterial mean pressure fell more with prazosin (7 ±1 vs 3 ±2 mmHg, $P < 0·01$). The increase in left ventricular stroke work was also similar (4·05 ±2·28 vs 5·67 ± 2·01 g m per m^2, NS), but arterial systolic pressure-heart rate product decreased more with prazosin ($P < 0·05$). The effects of the oral vasodilators on the relation between filling pressure and stroke work also differed (Fig.).

CLINICAL EFFECTS

All patients tolerated treatment with nitroprusside and oral vasodilators without any major side effects during the study. With prazosin two patients had nausea initially which gradually disappeared. Two other patients developed mild headache while receiving hydralazine and required aspirin for relief. No episodes of hypotension, tachycardia, or myocardial ischaemia (angina or ST segments changes) were observed in any patient. In five patients, diastolic gallop disappeared and basal râles decreased with both prazosin and hydralazine.

Discussion

Our study was designed to compare the acute haemodynamic effects of one parenteral and two oral vasodilator agents in the same patients with heart failure. Baseline clinical evaluation and haemodynamic recordings were made after the systemic and pulmonary arterial pressures and cardiac output had become stable with bed rest. Prazosin and nitroprusside were given in random sequence; hydralazine was given last to all seven patients. Though a sufficient time interval was provided between the different agents to allow the pressures and cardiac output to return to baseline level, it is possible that the residual effect of one agent may possibly have affected the actions of another. The fixed doses of prazosin (4 mg) and hydralazine (100 mg) were selected after preliminary studies in other patients with variable dose regimens.

Our results support previous observations (Franciosa *et al.,* 1972; Chatterjee *et al.,* 1973a; Guiha *et al.,* 1974) that intravenous nitroprusside produces haemodynamic improvement in patients with chronic heart failure: stroke work increases at a lower left ventricular filling pressure. In the same patients, orally administered prazosin (4 mg) resulted in a similar improvement in the relation between left ventricular filling pressure and stroke work, in association with a fall in systemic and pulmonary vascular resistance. Oral hydralazine (100 mg) also increased stroke work with a decrease in systemic vascular resistance. Compared with prazosin and nitroprusside, the fall in left ventricular filling pressure with hydralazine was minimal.

Even in the same patient, the mechanism of action of the three vasodilators appeared to be different. Nitroprusside, by direct action, dilates both arterial and venous beds equally, resulting in a decrease in afterload as well as preload (Miller *et al.,* 1976). Prazosin also has been shown to have a balanced dilator action on arterial and venous beds (Miller *et al.,* 1977). The actions of prazosin are mediated by vascular alpha-receptor blockade (Graham and Pettinger, 1979). Because of their similar vasodilator effects, intravenous nitroprusside and oral prazosin have similar afterload- and preload-reducing effects in patients with congestive heart failure (Mehta *et al.,* 1978a). Hydralazine, on the other hand, is a potent dilator of the arterial bed with only minimal effects on the venous bed (Franciosa *et al.,* 1977). In addition, hydralazine has a positive inotropic action (Khatri *et al.,* 1977). Because of the lack of a significant venodilator action, hydralazine administration does not decrease left ventricular filling pressure in patients with congestive heart failure, though systemic vascular resistance falls greatly (Chatterjee *et al.,* 1976b; Franciosa *et al.,* 1977; Mehta *et al.,* 1978b). Our study shows that the decrease in afterload induced by the two oral vasodilators (prazosin and hydralazine) in the same patients is similar.

The exact mechanism of the increase in cardiac output after vasodilator therapy in patients with heart failure is not known. It has been suggested (Sonnenblick and Downing, 1963; Cohn, 1973) that cardiac output increases as a result of increased myocardial fibre shortening in the failing ventricle consequent upon vasodilator-induced reduction in systemic vascular resistance. Indeed, in this study, the high systemic vascular resistance associated with chronic heart failure fell with all three vasodilator agents. We have shown that in the failing heart, the pulsatile flow component (characteristic impedance) of the vascular load is increased (Pepine *et al.,* 1978), in addition to the mean or steady flow component (systemic vascular resistance). These findings suggest that the compliance of the aorta is reduced in patients with heart failure. Preliminary studies in our laboratory show that in patients with heart failure nitroprusside decreases the pulsatile as well as the mean flow component of the vascular load (Pepine *et al.,* 1975). These observations suggest that the beneficial action of nitroprusside may be related to altered aortic compliance (Pepine *et al.,* 1975). The oral vasodilators compared in this study may also alter the distensibility of the aorta and thereby effect improved ventricular function by reducing the pulsatile component of vascular load. Inotropic actions of hydralazine (Khatri *et al.,* 1977) may also be partly responsible for increased cardiac output. Whatever the precise mechanism of action in patients with heart failure both oral agents compared in this study improved left ventricular function. Furthermore, this haemodynamic improvement was observed at doses that were well tolerated in these patients.

Comparison of the haemodynamic effects of a single dose of oral prazosin (4 mg) and of hydralazine (100 mg) with nitroprusside in the same patients with heart failure showed that the effects of prazosin were similar to those of nitroprusside. In a given patient, prazosin, like nitroprusside, effectively decreased left ventricular filling and pulmonary arterial pressures and increased cardiac output. Left ventricular stroke work increased less with oral prazosin than with intravenous nitroprusside. This may be because of the greater effectiveness of nitroprusside or the dose of prazosin used (Mehta *et al.,* 1978b). In contrast, oral hydralazine only increased cardiac output in the same patients. Though the increase in cardiac output was similar to that induced by prazosin, hydralazine caused no significant fall in left ventricular filling pressure. The absence of a significant fall in left ventricular filling and pulmonary arterial pressures with hydralazine may result from its lack of vasodilator effect on capacitance vessels (Chatterjee *et al.,* 1976b; Franciosa *et al.,* 1977; Mehta *et al.,* 1978b). We (Mehta *et al.,* 1978b) and others (Chatterjee *et al.,* 1976a; Pierpont *et al.,* 1978) have shown that a venodilator agent added to hydralazine lowers left ventricular filling pressure without altering cardiac output. Thus, hydralazine combined with a venodilator agent mimics the effects of intravenous nitroprusside; however, oral prazosin alone, like nitroprusside, improves left ventricular function.

Effective orally administered vasodilators are actively being sought for the management of ambulant patients with heart failure. This study shows that patients with the symptoms and signs of high left ventricular filling pressure and low cardiac output may benefit from the use of prazosin. On the other hand, hydralazine may be effective in those patients with low cardiac output but normal or only slightly increased left ventricular filling pressure.

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Comparison of single plane and biplane radionuclide ventriculograms performed in oblique projections in patients with acute myocardial infarction

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SUMMARY Thirty-five patients were studied by first pass radionuclide ventriculography in both right anterior oblique and left anterior oblique projections, after an acute myocardial infarction. Left ventricular ejection fraction was measured in both obliques from the background corrected time-activity curves and the values correlated closely. Mean left ventricular ejection fraction from the two obliques correlated well with that measured from the ventricular perimeters using a biplane area-length formula. End-diastolic volume from the single plane right anterior oblique correlated with that measured using the biplane formula. Combined right and left anterior oblique projections allowed identification of akinetic sites in all patients, whereas the right anterior oblique alone failed to delineate akinetic sites in 1/10 (10%) of patients with anterior infarction, 2/9 (22%) with inferior infarction, and 6/16 (37%) with multiple areas of infarction. The left anterior oblique alone identified akinesis in all patients with anterior infarction, but failed in 2/9 (22%) with inferior infarction and 5/16 (31%) with multiple sites of infarction. The mean percentage akinesis from both obliques showed a significant negative correlation with mean ejection fraction as did that from the right anterior oblique alone. Percentage akinesis from the left anterior oblique alone correlated less well with left ventricular ejection fraction. The combination of right and left anterior oblique radionuclide ventriculograms provides greater accuracy in the detection of akinetic segments, especially when multiple areas of infarction are present. The use of a single plane left anterior oblique alone may prove misleading in the quantification of wall motion abnormalities, and in this respect should be interpreted with caution.

Since the animal experiments of Tennant and Wiggers (1935), abnormal regional myocardial performance has been thought to be a cause of ventricular dysfunction. In 1967 Herman *et al.* showed conclusively that localised abnormalities of ventricular contraction could exist in man and suggested them as a cause of clinical cardiac failure. Feild *et al.* (1972) described a quantitative relation between the degree of myocardial damage, as assessed by biplane contrast cineangiography, and the presence of cardiac failure. The development of radionuclide techniques capable of providing information on both ejection fraction and regional wall motion has been a major advance, allowing the non-invasive acquisition of such data, and previous reports have indicated the applicability of radionuclide angiograms to the study of patients with myocardial infarction (Kostuk *et al.*, 1973; Rigo *et al.*, 1974; Schelbert *et al.*, 1976). In patients with ischaemic heart disease the right and left anterior oblique have been regarded as the optimum projections for assessing wall motion abnormalities (Cohn *et al.*, 1974), but isotope techniques that employ scanning of the radioactive cardiac blood pool with the aid of electrocardiographic gating devices are limited in the choice of projection, because of inadequate spatial separation of the ventricles which contain tracer simultaneously at equilibrium. In these cases, the left anterior oblique has been the projection of choice for wall motion analysis, though even then visualisation of the inferior and anterior walls of the left ventricle may be suboptimal when isotope is present simultaneously in both ventricles (Pierson *et al.*, 1977).

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The first pass radionuclide ventriculogram provides temporal separation of the cardiac chambers as counts are accumulated only during the initial passage of the tracer through the central circulation. The problem of overlap in the right anterior oblique is thus not present, and choice of projection is not a limiting factor.

On the basis of this, a study was undertaken to examine the ability of first pass radionuclide ventriculograms performed in both right and left projections to provide information on global and segmental ventricular function in patients with acute myocardial infarction.

Patients and methods

Thirty-five patients were studied between five and eight days after an acute myocardial infarction. There were 33 men and two women, with a mean age of 56, and an age range of 33 to 73 years. Myocardial infarction was diagnosed by the conventional criteria of typical history, evolution of electrocardiographic Q waves, and characteristic rise and fall of serum enzymes. The site of infarction was read from the patients' electrocardiograms by an independent observer, and studies were analysed either by a cardiologist or a trained technician unaware of the site of infarction. No patient was studied while still requiring acute coronary care.

Radionuclide ventriculography was carried out using a computerised multi-crystal gamma camera (Baird-Atomic, system 77) with high count rate capabilities (Budinger and Rollo, 1977). Studies were performed using a 1·5-inch parallel hole collimator. A bolus of high specific activity ^{99m}Technetium pertechnetate was injected into a medial vein of the right arm, followed by a rapid 20 ml saline flush, as previously described (Dymond *et al.*, 1979). Data were collected in frame mode at 0·05-second intervals for 50 seconds, stored on magnetic disc, and transferred from disc to magnetic tape for permanent storage. The first study was performed in the 30° right anterior oblique projection, and 10 to 15 minutes allowed to elapse so that adequate blood pool clearance of the first bolus could occur. The patient was then positioned in the 30° left anterior oblique projection with a 15° caudal tilt. Before the second bolus injection a static background frame was collected to a maximum of 9000 counts per cell. Immediately after this frame was obtained the second bolus of ^{99m}Technetium was injected, and counting again carried out for 50 seconds. A 10 mCi bolus was used for the first injection and 15 mCi for the second. The first study was corrected for the dead-time of the instrument using a manufacturer supplied computer programme, and for the field non-uniformity by automatically correcting each frame of data for differences between individual crystals, using a uniform flood source. The second study was corrected for residual blood pool activity as well as for dead-time and non-uniformity.

Analysis of each study was carried out by first replaying the study in the form of 12 serial images, each representing 30 summed 0·05 second frames and the left ventricular phase identified. A region of interest was drawn using a magnetic pen and grid array, the latter representing the detector's 294 crystals. A 0·05 second per frame time-activity curve was generated. Left ventricular ejection fraction was calculated for both obliques from the change in counts from end-diastole to end-systole, the counts in the ventricle being proportional to volumes at any one time. The formula for ejection fraction takes into account the contribution of background non-ventricular counts, background frames being chosen directly from the flat part of the left ventricular time-activity curve approximately 0·5 seconds before the peaks and troughs of the laevophase (Dymond *et al.*, 1979). This method for calculating ejection fraction makes no assumptions about ventricular shape. The peaks and troughs were then summed by the computer to provide one representative cardiac cycle, with high count rates for statistical accuracy. Ventricular perimeters for each oblique were generated by computer, using an isocount edge detection technique whereby the 5 per cent count band corresponding to 25 or 30 per cent of the maximum end-diastolic count per cell is enhanced. Perimeters for end-diastole and end-systole were superimposed. For the calculation of ventricular volumes, the formula of Greene *et al.* (1967) was applied to the right anterior oblique perimeters. For the combined right and left anterior oblique studies, volumes were calculated according to the method of Wynne *et al.* (1978), using the areas (A) of the cardiac chambers in both right and left obliques, and the long axes (L), the longest measured chord in any direction within the ventricular silhouette.

Thus volume in millilitres from both obliques

$$= 8/3\pi \times \frac{\text{Area (RAO)} \times \text{Area (LAO)}}{L_{\min}}$$

where $L_{\min}$ is the smaller of the two long axes from either left or right oblique. All areas and lengths were measured by tracing on to a pressure-sensitive pad linked to a computer and an algorithm analogous to planimetry, as previously described

(Dymond *et al.,* 1979). In addition the extent of akinesis produced by the infarction was measured by expressing the length for which the end-diastolic and end-systolic perimeters were exactly superimposed, indicating no inward wall motion, as a percentage of the total end-diastolic circumference (Feild *et al.,* 1972).

Results

Ten patients had suffered anterior infarction, nine inferior, and 16 patients were judged to have multiple areas of infarction. Ejection fraction calculated from the time-activity curve of the right anterior oblique study ranged from 20 to 71 per cent, with a mean of 39·4 per cent. The values from the left anterior oblique projection ranged from 20 to 60 per cent, with a mean of 34·2 per cent. Fig. 1 shows the relation between these two independently obtained values. There is a good correlation with a coefficient of 0·85 which is highly significant ($P < 0{\cdot}001$). Analysis of the regression line by Student's t test indicates that the slope is significantly different from one and that the values of ejection fraction obtained from the left anterior oblique (LAO) are significantly lower than that from the right anterior oblique (RAO), with a regression equation:

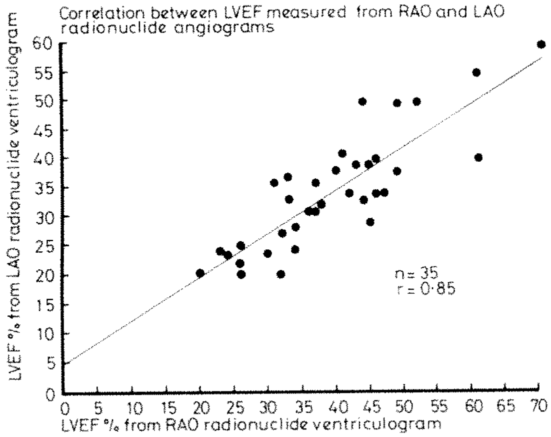


Fig. 1 *Correlation between ejection fractions (LVEF) measured independently from time-activity curves for right anterior oblique (RAO) and left anterior oblique (LAO) studies.*

$$\text{LVEF (LAO)} = 0{\cdot}757\ \text{LVEF (RAO)} + 4{\cdot}378.$$

The intercept of the graph is not significantly different from zero.

Fig. 2 shows the correlation between the mean ejection fraction from the two obliques and the ejection fraction obtained from the biplane geometric formula. In the 27 patients in whom adequate measurements could be made, the correlation is significant, with a coefficient of 0·89 ($P < 0{\cdot}001$). Analysis of this graph by Student's t test showed that the slope did not vary significantly from one and the intercept did not vary significantly from zero.

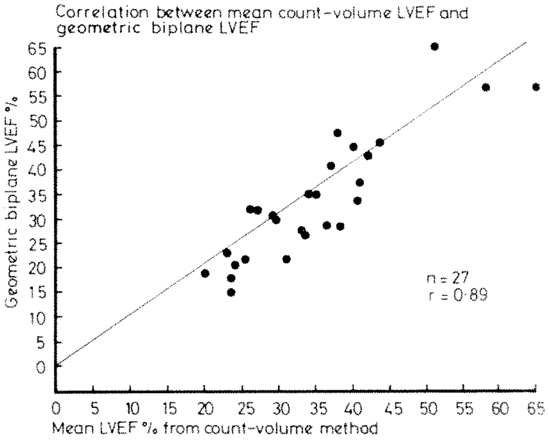


Fig. 2 *Correlation between mean ejection fraction (LVEF) obtained from the left anterior oblique (LAO) and right anterior oblique (RAO) study, with that measured from ventricular perimeters of both obliques.*

End-diastolic volume measured from the biplane formula correlated closely with the volume from the single plane right anterior oblique ($r = 0{\cdot}88$, $P < 0{\cdot}001$), as shown in Fig. 3. Despite the

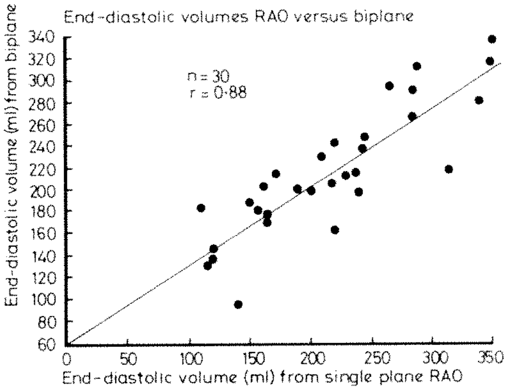


Fig. 3 *Correlation between end-diastolic volume measured from the single plane right anterior oblique with that measured from both obliques.*

significant regression coefficient, there was distinct disparity between the absolute values for volumes, with a regression equation of $y = 0{\cdot}716x + 62{\cdot}6$.

For the purpose of wall motion analysis, five ventricular segments were considered as described by Cohn *et al.* (1974). The right anterior oblique was used to identify three segments, namely anterior, apical, and inferior. The left anterior oblique was able to provide information on two segments, septal and posterolateral. The comparative ability of either oblique to detect akinesis is shown in Table 1.

Table 1 *Comparative ability of single plane and biplane projections to detect akinesis in anterior, inferior, and multiple infarctions*

Infarct	*Number*	*RAO*	*LAO*	*Biplane*
Anterior	10	9	10	10
Inferior	9	7	7	9
Combined	16	10	11	16

RAO, right anterior oblique; LAO, left anterior oblique.

Of 10 patients with anterior infarction, the right anterior oblique projection detected akinesis anteriorly in nine (90%), whereas the left anterior oblique projection successfully identified akinesis in all 10. The right anterior oblique alone and the left anterior oblique alone each demonstrated akinesis in seven of the nine (78%) with inferior infarction, the left anterior oblique showing akinesis in the lower part of the posterior wall and apex. Combination of the two obliques allowed identification of akinetic sites in all nine.

In 16 patients with multiple sites of infarction, the right anterior oblique demonstrated akinesis in more than one segment in 10 (62%), the left anterior oblique in 11 (68%), and the combined projections were successful in all 16 cases.

Fig. 4 is an example of right anterior oblique and left anterior oblique radionuclide ventriculograms in a patient with anterior and posteroinferior infarction electrocardiographically. The left-hand image is the superimposed perimeters of the right anterior oblique study, the right-hand image the left anterior oblique. The end-diastolic perimeter is shown in each case in blue, the end-systolic perimeter in yellow. The right anterior oblique study shows an area of akinesis anteriorly, while the inferior region shows definite inward motion in systole. The left anterior oblique shows the posterolateral wall to be totally akinetic, whereas the septum shows motion in systole. Thus each projection identified an area of akinesis exclusively, and the complete information on segmental wall motion would not have been obtained from a single projection alone.

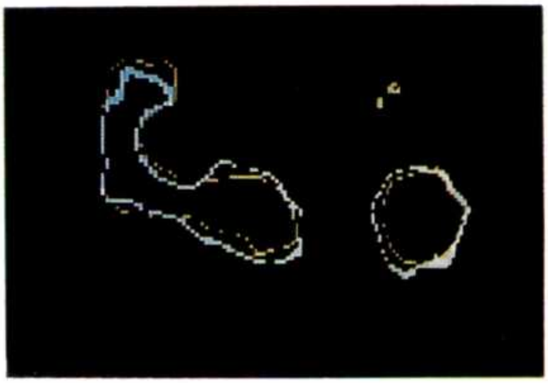


Fig. 4 *Perimeters of the right anterior oblique (RAO) (left-hand image) and left anterior oblique (LAO) radionuclide ventriculograms from a patient with anterior and posteroinferior infarction. End-diastolic perimeter is in blue; end-systolic perimeter in yellow. RAO only shows akinesis anteriorly, the LAO only posterolaterally.*

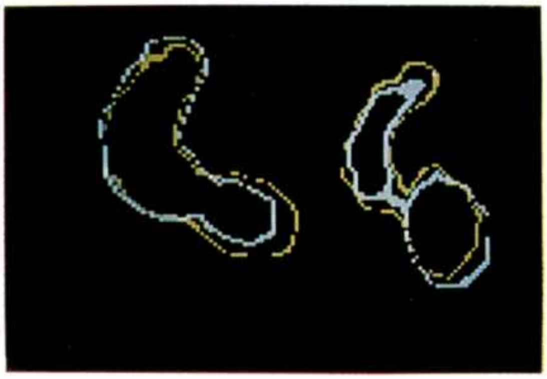
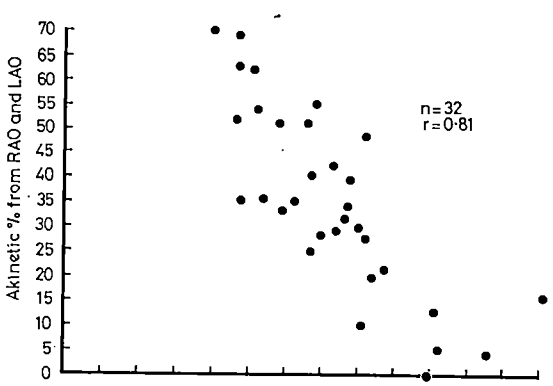


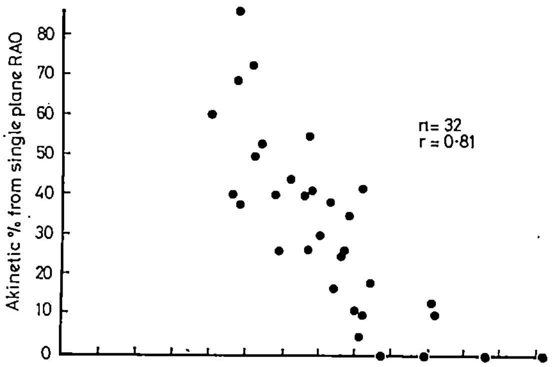
Fig. 5 *Perimeters of the right anterior oblique (RAO) (left-hand image) and left anterior oblique (LAO) radionuclide ventriculograms from a patient with localised anteroseptal infarction. No akinesis on RAO, but small area of akinesis shown septally on LAO.*

Fig. 5 is an example of a right and left anterior oblique study in a patient with localised anteroseptal infarction electrocardiographically. The left-hand image, the right anterior oblique, shows no akinesis, whereas the left anterior oblique study shows a small area of akinesis septally.

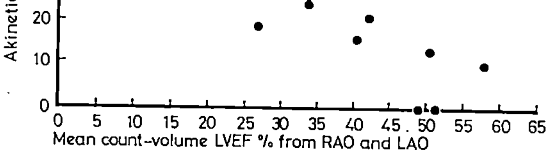
The relation between the extent of akinesis from each study and the degree of depression of overall ventricular function as measured by ejection fraction, is shown in Fig. 6a, 6b, and 6c. In Fig. 6a the



a Correlation between mean akinetic length and mean LVEF



b Correlation between akinetic % from single plane RAO and mean LVEF



c Correlation between LAO akinetic % and mean LVEF

Fig. 6 *Relation of mean ejection fraction from two obliques (LVEF) to* (a) *akinetic percentage (mean derived from RAO and LAO;* (b) *akinetic percentage from single plane RAO; and* (c) *akinetic percentage from single plane LAO.*

mean ejection fraction and akinetic percentage from the two obliques are plotted for 32 patients. There is a significant negative correlation with a coefficient of 0·81 ($P<0·001$). Mean ejection fraction and akinesis from a single plane right anterior oblique are plotted in Fig. 6b. Again, there is a significant negative correlation with an identical coefficient as for the biplane study ($r=0·81$, $P<0·001$). Analysis of the relation between the two indices for the single plane left anterior oblique yielded a much less good correlation, with a coefficient of 0·58 ($P<0·005$) and a large amount of scatter (Fig. 6c).

For the entire patient population percentage akinesis from the right anterior oblique was 31·9 ±22·6 per cent (mean ± standard deviation), and for the left anterior oblique the value was 39·6 ±20·5 per cent. This difference is statistically significant ($P<0·05$) suggesting that the left anterior oblique overestimates the extent of akinesis compared with the right anterior oblique. Table 2 shows the mean percentage akinesis with standard deviations, in patients with different sites of infarction. In none of the three subgroups, inferior, anterior, or multiple infarction, did the differences in mean akinetic percentage reach statistical significance despite the large discrepancies between the means from the two obliques in patients with inferior and multiple infarctions.

Table 2 *Comparison of percentage akinesis from two obliques for whole group and for anterior, inferior, and multiple infarctions*

	RAO (mean ± SD)	*LAO (mean ± SD)*
Inferior infarct	15·4 ±14·6%	28·4 ±25·5% (NS)
Anterior infarct	33·1 ±17·8%	32·2 ±14·9% (NS)
Multiple infarcts	38·5 ±25·1%	49·8 ±14·9% (NS)
Whole group	31·9 ±22·6%	39·6 ±20·5% ($P<0·05$)

RAO, right anterior oblique; LAO, left anterior oblique; SD, standard deviation.

Percentage akinesis was greatest in those with multiple infarctions whether from the right anterior oblique or left anterior oblique, and similarly both projections showed a greater percentage akinesis in patients with anterior infarction than in those with inferior infarction. Analysis of these differences by a non-paired t test showed that for both the right and the left anterior oblique, akinesis in anterior infarction failed to be significantly greater than that in inferior infarction. For the right anterior oblique, percentage akinesis was not significantly higher in multiple than in anterior infarction, though the difference between multiple and inferior infarction did achieve significance ($P<0·02$). For the left anterior oblique, however, percentage akinesis was significantly greater for multiple than for anterior infarction ($P<0·02$), and for inferior infarction ($P<0·02$).

Discussion

Several previous studies have pointed out the value of radionuclide techniques in the evaluation of patients with myocardial infarction. The right anterior oblique projection has been utilised for measurements of ejection fraction from time-activity curves (Steele *et al.,* 1974; Henning *et al.,* 1975; Schelbert *et al.,* 1976), but the two latter studies employed radarkymography for wall motion analysis. Kostuk *et al.* (1973) described the detection of wall motion abnormalities in the left lateral projection using peripheral venous injection of tracer. However, it is well recognised that in patients with ischaemic heart disease the right anterior oblique and left anterior oblique projections are the optimal for studying regional abnormalities of wall motion (Cohn *et al.,* 1974; Miller *et al.,* 1974). Gated blood pool scanning has been performed in right and left anterior oblique projections in patients with infarction (Rigo *et al.,* 1974) and ejection fraction and wall motion quantified, though no comparison was made between the right and left anterior oblique in that study. Because of the anatomical overlap of right and left ventricles in the right anterior oblique, changes in radioactive counts over the left ventricular region of interest will contain some data from the right ventricular blood pool when gated equilibrium imaging is employed in the right anterior oblique (Pierson *et al.,* 1977). The first pass radionuclide ventriculogram, by providing temporal separation of the ventricles, theoretically eliminates the contribution of right ventricular counts to the left ventricular time-activity curve. Previous reports have described contrast angiographic correlations of right anterior oblique radionuclide studies using the multicrystal gamma camera, which has the ability to accumulate enough counts during the first pass to provide statistically accurate data on wall motion (Bodenheimer *et al.,* 1978; Dymond *et al.,* 1979). It was not the purpose of this study to relate the angiograms of individual patients to clinical status, as it is already well recognised that the extent of left ventricular damage is related to functional capacity (Feild *et al.,* 1972). Instead, an attempt has been made to compare the right and left anterior obliques and to examine the ability of the combined projections to provide clinically relevant information.

The correlation obtained between ejection fraction measured independently from the two obliques is similar to that found by Bodenheimer *et al.* (1978), though these workers employed a 35 per cent background subtraction to the right anterior oblique time-activity curve on the basis that this provided the best correlation with left anterior oblique ejection fraction. In this present study no such standard background subtraction was used, rather the subtraction was carried out on each individual time-activity curve as described above. Marshall *et al.* (1977) found that ejection fraction from the anterior view was significantly higher than that from the left anterior oblique, using a similar background correction as was used in this study. The difference, as in this study, may well be related to variations in the efficiency of detecting background radioactivity from the lungs and the left atrium in the two positions. It is also possible that in the right anterior oblique some lag of activity in the right ventricle may contribute to the background portion of the time-activity curve and thus the background may be overestimated leading to an inappropriately high ejection fraction. In the left anterior oblique the spatial separation between the ventricles would preclude this. The main assumption in this method of background correction is that the background remains *relatively* constant during the left ventricular phase, compared with the gross fluctuation in counts between diastole and systole. This assumption is supported by the results of Van Dyke *et al.* (1972). The theoretical objections to the assumption appear to be of little importance practically in view of the previous good correlations obtained with ejection fraction measured by contrast angiography. Indeed, though it might be logical to expect the left anterior oblique to provide the closer correlation with contrast angiography in view of the problems with background, this is not always the case (Garcia *et al.,* 1977).

Calculation of ejection fraction by area-length formulae depends on the assumption that the ventricle conforms to certain geometric shapes, whereas ejection fraction measured from changes in radioactive counts does not. Mean ejection fraction from the count-volume method correlated well with that calculated from the biplane geometric formula applied to the ventricular perimeters. Recently, volumes calculated from biplane oblique ventriculography have been shown to correlate well with true volumes measured from human ventricular casts (Wynne *et al.,* 1978). In the present study the correlation between count-volume ejection fraction and biplane geometric ejection fraction was close, varying by 10 per cent or more in only three patients. This suggests that a biplane formula can be applied to radionuclide ventriculograms as well as contrast angiograms. It is possible that a closer correlation might have been obtained by varying the obliquity of the left anterior oblique and the degree of forward tilt, manoeuvres which alter the long axis of the left anterior oblique and hence calculated volume (Wynne *et al.,* 1978). Though no patient in our series underwent contrast angiography, a previous study has shown a close correlation between a geometric ejection fraction from the right and left anterior oblique gated blood pool scans and contrast angiographic ejection fraction (Garcia *et al.*, 1977).

Measurement of absolute left ventricular volume has become a standard technique in the assessment of left ventricular function (Rackley, 1976), and volumes calculated from radionuclide ventriculograms have been shown to correlate with volumes measured from contrast angiograms (Strauss *et al.*, 1971; Kostuk *et al.*, 1973), though in the right anterior oblique radionuclide volumes may overestimate the values compared with contrast angiograms (Dymond *et al.*, 1979). Results in this study suggest that a single plane right anterior oblique will overestimate end-diastolic volumes compared with biplane values when large volumes are present. This finding is in agreement with the contrast data of Cohn *et al.* (1974) in which the most disparity occurred in patients with asynergy, such as the group described here, despite significant correlation coefficients. Indeed, the regression equation in Cohn's series for patients with coronary artery disease and ventricular asynergy was almost identical to the equation from our own data. Wynne *et al.* (1978) also found that the biplane study led to less of an overestimation of true volume than a single plane right anterior oblique projection. The accurate assessment of end-diastolic volume is of clinical relevance given the finding of Rigo and coworkers (1974) that end-diastolic volume was only increased in infarct patients when left ventricular filling pressure was increased and cardiac index reduced, findings which relate to prognosis (Mathey *et al.*, 1974).

For the detection and localisation of infarction, akinetic segments from the radionuclide ventriculograms were correlated with the patients' electrocardiograms. The latter have been previously shown to be reliable in defining site of infarction demonstrated angiographically (Miller *et al.*, 1974). In the patients with anterior infarction the right anterior oblique missed akinesis on the one patient with localised anteroseptal infarction (Fig. 5), whereas septal akinesis was detected in all 10 on the left anterior oblique projection. In inferior infarction the left and right anterior oblique projections each detected seven of nine akinetic segments. The two with no akinesis on the right anterior oblique projection had electrocardiographic changes of posteroinferior infarction, and had posterior akinesis on the left anterior oblique projection. Posterior changes would not be detected on the right anterior oblique projection. Of the seven with no posterior changes electrocardiographically, all had inferior akinesis on the right anterior oblique and two had no akinesis on the left anterior oblique. Where posterior infarction occurs, therefore, the left anterior oblique may prove superior to the right anterior oblique, whereas the converse may be true if inferior wall abnormalities predominate. In fact Cohn *et al.* (1974) found normal left anterior oblique ventriculograms in all five patients with inferior infarction who had asynergy in the right anterior oblique projection. It is possible that the addition of hypokinesis or dyskinesis as criteria for abnormal wall motion might alter the detection rate for the two projections (Miller *et al.*, 1974), and recent reports have indicated that hypokinesis as well as akinesis can be shown from radionuclide ventriculograms (Bodenheimer *et al.*, 1978). This hypokinesis has been well correlated with asynergy from contrast ventriculograms in the right anterior oblique but not the left anterior oblique. In patients with combined areas of infarction, biplane views identified multiple akinetic sites in every case whereas each single plane had a substantial failure rate to detect more than one infarcted segment. Thus, biplane radionuclide ventriculography is more likely to be beneficial in patients with the greatest amount of asynergy, a finding in agreement with that of Cohn *et al.* (1974).

The extent of akinesis from radionuclide ventriculograms has been previously shown to correlate closely with that from contrast angiograms (Rigo *et al.*, 1974; Dymond *et al.*, 1979). For both right and left anterior oblique projections multiple infarctions produced greater akinesis than anterior infarctions, which in turn had more akinesis than inferior infarctions. These findings are in agreement with those from contrast angiographic data (Feild *et al.*, 1972; Miller *et al.*, 1974) and suggest that more myocardial damage occurs after anterior infarction than after inferior infarction (Sobel *et al.*, 1972). That the differences between the extent of akinesis for anterior and inferior infarctions failed to reach statistical significance in this study is partly related to the small numbers in the groups and the large variability in segment size. Our results in this report are similar to those of Feild *et al.* (1972) though in this latter study biplane ventriculography was carried out in the anteroposterior and lateral projections which are not the best projections for assessing asynergy.

A quantitative relation between the size of an akinetic segment and ejection fraction has been described in the experimental animal (Pairolero *et al.*, 1970) and in man (Feild *et al.*, 1972; Rigo *et al.*, 1974) but no study has compared results from different projections.

The advent of the non-invasive radionuclide ventriculogram has produced the potential for simple, safe acquisition of data on ventricular function in a wide variety of diseases. Limitations in choice of projection for technical reasons mean that the advantages and limitations of each projection must be precisely defined to avoid misinterpretation of data. It is evident from the graphs in Fig. 6 that the relation between ejection fraction and akinetic percentage is superior for the biplane or single plane right anterior oblique than for left anterior oblique. The significant difference between extent of akinesis for the left anterior oblique and right anterior oblique suggests that the left anterior oblique will tend to overestimate the extent of myocardial damage. This may be partly attributable to the fact that in the left anterior oblique the view is from the apex of the ventricle rather than perpendicular to the long axis, leading to a foreshortening effect. This potential limitation in the ability of the left anterior oblique to quantify the extent of akinesis should be borne in mind when the left anterior oblique projection is used alone in gated blood-pool scanning. The correlation coefficients obtained from the single plane right anterior oblique and the biplane are identical (0·81) and are similar to the correlations obtained by Feild *et al.* (1972) and Rigo *et al.* (1974). One limitation in this relation of akinetic segment size to depression of overall function is that no consideration is given to the function of the non-akinetic muscle. If the latter is normal the ejection fraction may be maintained at a higher level than if it were hypokinetic. Secondly, since measurements were performed in two projections in two dimensions, the akinetic percentage can only be an estimate of the true akinetic area of the left ventricle. Despite these limitations, the extent of akinesis is a reflection of the size of an infarct. With the evidence that infarct size is an important factor in prognosis (Sobel *et al.*, 1972), radionuclide ventriculography may become a new scintigraphic approach to the problem of assessing infarct size.

In summary, right anterior oblique and left anterior oblique first pass radionuclide ventriculograms performed on patients in the convalescent phase of acute myocardial infarction can provide information on ejection fraction and absolute ventricular volumes, as well as allowing visualisation of all areas of the left ventricle. The detection of abnormally contracting segments is superior for the combined projections than for a single plane study, a factor especially important in patients with multiple areas of infarction electrocardiographically. The ability of this non-invasive technique to relate derangements of ventricular structure to those of ventricular function provides a rational basis for the use of 'biplane' radionuclide ventriculography in the assessment of patients with acute myocardial infarction.

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Mitral valve apparatus
A spectrum of normality relevant to mitral valve prolapse

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SUMMARY The intricate anatomy of the mitral valve apparatus suggests that variations in its architecture may have functional significance. In this study, therefore, deviations from a basic scheme of normality of chordal support have been documented, with particular reference to the occurrence of deficient chordae. Chordae were considered as deficient when they had an irregular branching pattern, not compensated by neighbouring chordae, leaving parts of the valve leaflets less well supported than others. One hundred 'normal' heart specimens were studied, in which the mitral valve in the unopened state showed a regular appearance, and compared with 40 hearts in which the valve showed a deformity, classified as ballooning in 38 cases and as prolapse in two.

Deficient chordae were identified in eight of the 100 'normal' hearts and in 36 of the 40 hearts with a valve deformity. In the latter group the chordal deficiency was directly related to the leaflet deformity present. Deficiencies in chordal branching and distribution affected commissural chordae and rough zone chordae, showing a particular preference for the posteromedial commissural area and the middle scallop of the posterior leaflet. The latter abnormalities showed a tendency to be associated with finger-like posteromedial papillary muscle groups and a haphazard arrangement of chordal take-off. Both specimens with necropsy evidence of prolapse had such an arrangement.

The findings showed that there is a 'spectrum of normality' with respect to the anatomy of the mitral valve chordal apparatus. It provides an anatomical basis for echocardiographic recordings of disharmonious mitral valve movements, frequently recorded among otherwise healthy individuals. Moreover, it is assumed that such minor variations may play a role in the pathogenesis of the syndrome of mitral valve prolapse, by rendering unsupported parts of leaflets particularly vulnerable to high pressures.

The functional anatomy of the mitral valve apparatus has been well documented in recent years and it is at present widely acknowledged that disturbances in co-ordinated interaction of the various anatomical components may underlie valve insufficiency (Perloff and Roberts, 1972). For obvious reasons most interest in this field has been generated by the effects of myocardial ischaemia. However, considering the intricate architecture and the delicate interplay necessary for proper function, it can be anticipated that variations in anatomy may also become of importance. It is surprising, therefore, that little attention has been given to this particular aspect of the functional anatomy of the mitral valve apparatus.

When establishing a concept of 'normality' for the mitral valve the studies of the Toronto group of investigators may serve as a point of departure (Lam *et al.*, 1970; Ranganathan *et al.*, 1970). They presented a scheme and classification for the normal arrangement of both mitral valve chordae and leaflets and mention that variations in morphology were not infrequent. Our initial experience was in keeping with their basic scheme but we became particularly aware of the potential functional significance of 'minor' variations in chordal distribution encountered within their basic scheme of normality. The nature of some of these variations was such that some parts of the mitral valve leaflets seemed less well supported than others. It seemed that this observation could be of significance regarding mechanisms for mitral valve prolapse, since echocardiographic studies indicate that abnormal valve movement is often found among apparently healthy subjects (Markiewicz *et al.*, 1976; Procacci *et al.*, 1976). In view of these

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considerations, the mitral valve apparatus has been studied in 140 necropsy specimens, in an attempt to evaluate the significance of variations in chordal distribution for the occurrence of deformities in the valve leaflets.

Subjects and methods

Hearts were obtained from necropsies on patients who had died from causes unrelated to cardiac disease. In none had a mitral valve disorder been noticed during clinical examination, but they had not been seen by a cardiologist.

Hearts were excluded which showed necropsy evidence of rheumatic or infectious valve diseases, calcified mitral ring, or conditions known to affect intrinsically the connective tissues, such as Marfan's disease or mucopolysaccharidoses.

The study was based on 140 heart specimens, examined in the fresh state. In all instances the left ventricle was filled with tap water, through a cannula in the aortic ostium, after tying the ascending aorta. The pressures mounted to an approximate 200 mmHg. The hearts were then divided into two discrete groups. The first group consisted of 100 mitral valves which, when observed from the left atrium with the left ventricle unopened, neatly closed the mitral orifice. Usually, such leaflets show *hoods,* defined as an upward bulging of interchordal leaflet tissues. The degree of hooding may vary from one individual to the other, but there is a tendency for them to be more pronounced in the elderly and in conditions that lead to left ventricular hypertrophy. This suggests that hooding is an acquired phenomenon rather than a basic aspect of 'normality'. However, because of the occurrence of hoods in nearly all hearts this finding was considered 'normal'. The 'normal' hearts were obtained from 62 male and 38 female patients; the ages varied from 23 to 92 years, with an average of 61 years.

The second group consisted of 40 heart specimens in which a deformity of the mitral valve was present as observed from the left atrium. The abnormality most frequently encountered was termed *'ballooning deformity',* defined as the condition in which a leaflet, or part of a leaflet, showed an upward bulging extending beyond that of the 'normal' interchordal hoods. Moreover, the degree of bulging towards the left atrium was greater than that seen with hoods. However, when the two mitral valve leaflets were brought into apposition there was no actual overshoot in the postmortem state. This was in contrast to the condition in which the aforementioned procedure resulted in an actual overshoot of the free margin of the affected leaflet, which has been considered as valve *prolapse.* The ballooning deformities were encountered in all 40 specimens, while an additional prolapse was present in two hearts. These abnormal hearts were obtained from 23 male and 17 female patients; the ages varied from 38 to 86, with an average age of 63 years.

In each of the 140 specimens a close study was made of the architecture of the chordae, taking the basic scheme of normality defined by the Toronto group (Lam *et al.,* 1970; Ranganathan *et al.,* 1970) as the point of departure (see below). The study has focused in particular on the occurrence of chordae exhibiting a deficient branching pattern, *without* sufficient overlap of neighbouring chordae, an arrangement leaving part of a leaflet apparently less well supported than would be expected from 'normality'. The term *deficient chorda* will be used for this particular arrangement.

BASIC SCHEME OF NORMALITY

A basic scheme of 'normality' of the mitral valve was based on the work of the Toronto group of investigators (Lam *et al.,* 1970; Ranganathan *et al.,* 1970). They introduced a classification of chordae, relevant to mitral valve function, by distinguishing two major sets of chordae. Firstly, they introduced the term 'commissural chordae' for the cords which support the anterolateral and the posteromedial commissural areas. In the 'typical' situation there is one cord for each commissure (Fig. 1). It arises as a single main stem from the underlying papillary muscle group, and then branches into fan-like structures which insert into the free margin of the two commissural leaflets (Fig. 1C). The lateral spread of these branches is wider in the posteromedial commissural area than it is at the anterolateral commissure. The commissural chordae are considered to play a major role in the process of folding and unfolding of the leaflets bordering on the commissure. Lam and associates (1970) mentioned the absence of one anterolateral commisural chorda among their 50 hearts, but they did not expand on the occurrence of 'atypical' commissural chordae with a deficient branching pattern.

The second set of chordae, as defined by the Toronto workers, is formed by a group of 'leaflet chordae'. Within this group the 'rough zone chordae' are the ones which give the major support to both the anterior and posterior leaflets. In the 'typical' situation each 'rough zone chorda' divides into three separate cords, shortly after the origin of the main stem from the papillary muscle (Fig. 1E). One of these cords inserts into the free margin of the leaflet, while the second and third cord insert beyond the free margin, reinforcing the site of the

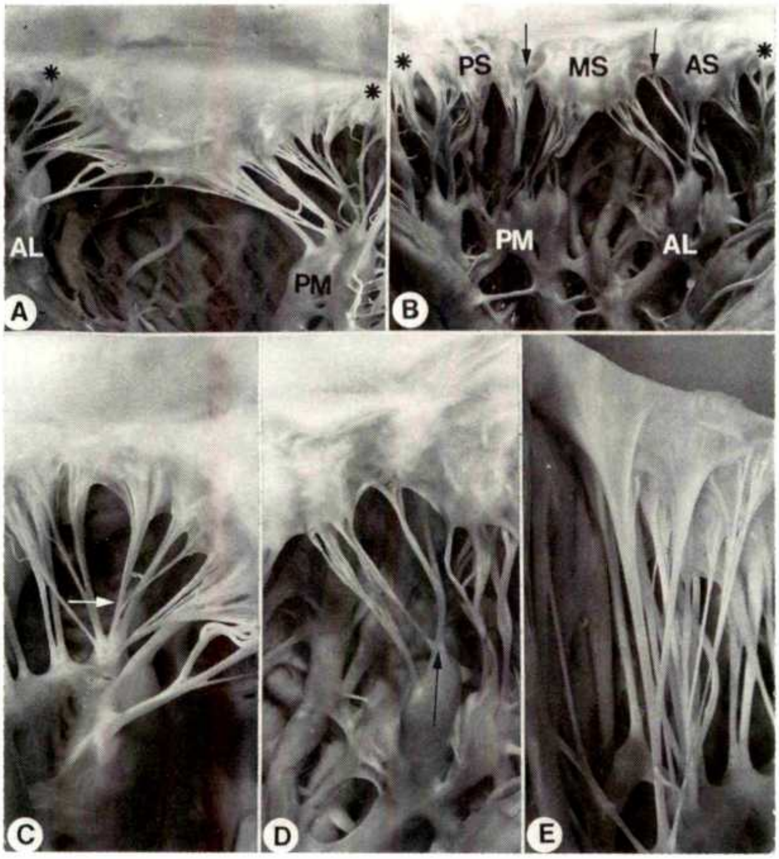

Fig. 1 *Display of the basic scheme of normality of the mitral valve from heart specimens.* (A) *The anterior leaflet viewed from the back with the left ventricle opened. Rough zone chordae originate from both the anterolateral (AL) and posteromedial (PM) papillary muscle groups and insert into the corresponding halves of the leaflet. The commissural sites are indicated by asterisks.* (B) *The posterior leaflet viewed from the front after opening the left ventricle and division of the anterior leaflet. Rough zone chordae originate from the anterolateral (AL) and posteromedial (PM) papillary muscle groups. In this specimen there are three scallops, a middle scallop (MS), flanked by a posteromedial commissural scallop (PS), and an anterolateral commissural scallop (AS). The commissural sites with the anterior leaflet are indicated by asterisks. The two clefts are indicated by arrows. Note in both (A) and (B) the 'hoods' present in the rough zone area.* (C) *A typical commissural chorda* (arrow), *in this instance for the anterolateral commissure, which after its origin from the tip of the papillary muscle fans out, inserting into the free margin of the leaflet.* (D) *A typical cleft chorda* (arrow), *which divides into branches inserting into the free margin and the more basal aspect of the leaflet.* (E) *A typical rough zone chorda, which shortly after its origin divides into three branches with terminal additional ramifications just before their insertion into the rough zone area of the leaflet.*

line of closure. Among the rough zone chordae for the anterior leaflet there is a thickened 'strut' chorda, one from each papillary muscle inserting into the corresponding half of the leaflet. The rough zone chordae are considered to be of major significance in maintaining the integrity of the valve during systole and should therefore exhibit a regular distribution over the anterior and posterior leaflets. However, Lam and associates (1970) reported the occurrence of so-called 'atypical' rough zone chordae, which they defined as cords exhibiting a deficient branching, albeit that at the sites of insertion an overlap from neighbouring chordae took place in a high percentage of cases. These investigators observed 'atypical' chordae among 37 of their 50 hearts.

The cleft chordae, delineating the clefts which accentuate the scallops of the posterior leaflet, were considered as a separate entity within the group of leaflet chordae. They insert into the free margin as well as the rough zone areas of the two scallops bordering on the cleft, so that from a functional point of view they probably act like rough zone chordae (Fig. 1D). For the purposes of this study we have included them in the latter category. Basal chordae constitute the final type within the group of leaflet chordae, present only for the posterior leaflet. These cords originate from the ventricular free wall and usually fan out just before their insertion into the basal aspect of the posterior leaflet, close to the annulus fibrosus. This arrangement suggests that they reinforce the basal part of the leaflet during systole, but their immediate functional significance seems limited. Lam and associates (1970) found basal chordae in only 31 of their 50 hearts, while their number and location showed considerable variations. For these reasons we have not included basal chordae in our studies.

Results

Of the 100 normal hearts there were 61 in which the basic arrangement of the chordae was designated as normal; 39 hearts showed a variation within the basic scheme. In 31 of these 39 specimens a sufficient overlap of neighbouring chordae was present, leaving a total of eight normal hearts with deficient chordae. In all of these eight hearts the deficient chordae supported the anterior leaflets.

Of the 40 hearts with a pronounced valve deformity, all showed a variation in chordal arrangement, which in four instances seemed to be compensated by neighbouring cords. In other words, 36 of these 40 hearts (90%) showed deficient chordae. In all instances the observed deficiency showed a direct topographic relation with the valve deformity. In the four hearts where no deficient chordae could be identified, we observed ballooning deformity of the middle scallop of the posterior leaflet. The deficient chordae were distributed as follows.

COMMISSURAL CHORDAE

Deficient commissural chordae were identified only among the 40 hearts with a grossly identified leaflet abnormality. In each instance the valve had a ballooning deformity. Nine specimens presented such a deficient chorda, affecting the posteromedial commissure in seven and the anterolateral commissure in two cases.

Two major aberrations in architecture were identified. The first abnormality was characterised by a commissural chorda which, after a basically normal origin, showed an irregular and deficient branching pattern. This particular arrangement in itself was not infrequent among normal hearts either, but sufficient overlap from rough zone chordae restored a regularly distributed support. The commissural chordae reported here lacked such additional support, rendering part of the leaflets relatively unsupported (Fig. 2A and B). The second form was characterised by a profoundly shortened chorda, showing only sparse ramifications which inserted at the site of the deepest indentation of the commissure. Thus an extensive area of free margin was left without chordal insertions (Fig. 2C and D).

Superficial examination of these chordal aberrations may suggest a similarity with a post-rheumatic process (Fig. 2A and D). However, close inspection will reveal that most chordae are slender or fan-like, and that the main abnormality is not one of chordal fusion but of chordal deficiency. The associated valve leaflet shows a localised tissue response composed of scar tissue, but such reparative processes are in themselves non-specific and cannot be interpreted as favouring a rheumatic origin.

ROUGH ZONE CHORDAE

Deficient rough zone chordae were present in eight of the 100 normal hearts and in all 40 hearts showing a valve deformity. Such anomalies affected both the anterior and posterior leaflets.

Anterior leaflet

In all the eight 'normal' valves in which deficient chordae were detected, these had supported the anterior leaflet. The lateral and medial halves of the anterior leaflet were involved in three and five instances, respectively. Of the 40 deformed valves, 26 showed such a deficiency in chordal distribution for the anterior leaflet. In nine instances the lateral half of the leaflet was involved, while in 17 cases the anomaly related to the medial half.

Between both groups there were no major differences regarding the type of chordal anomaly. Basically, the deficiency encountered was caused by one of two major aberrations. Firstly, a strut chorda was present, but it was not accompanied by the usual neighbouring slender rough zone chordae, leaving a 'bare' area not supported in the usual way (Fig. 3A and B). In some instances this thick and deficient strut chorda contained muscle extending from the papillary muscle. The chorda could thus be designated as a persistent muscular chorda, but its categorisation in this series was based on its deficient branching pattern rather than its specific build. The second type consisted of an irregular grouping of slender chordae, usually crowding close to the free margin of the leaflet, leaving the more distal part of the 'rough zone area' with less chordal

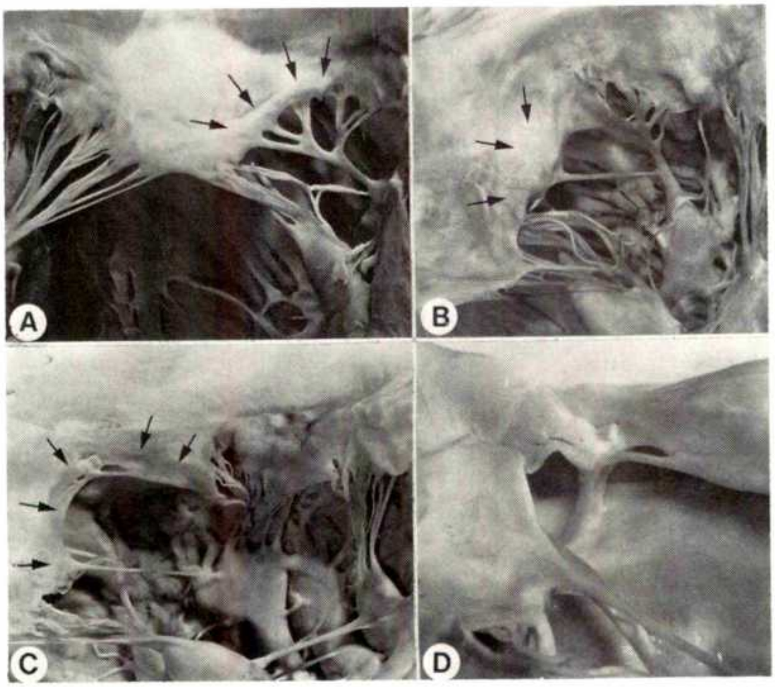

Fig. 2 *Examples of deficient commissural chordae.* (A) *An abnormal posteromedial commissural chorda with an irregular insertion. The corresponding area of the anterior leaflet shows an upward bulging and apparent thickening of the leaflet* (arrows). (B) *A similar situation in which deficient branching of the posteromedial commissural chorda is associated with a localised valve deformity* (arrows). (C) *A highly deficient commissural chorda which renders a large area of the medial half of the anterior leaflet and part of the posteromedial commissural scallop unsupported* (arrows). *A detail of this 'stump' chorda, from a slightly different angle, is shown in (D). Note the subtle differences between mitral valve leaflets with deficient chordae and the abnormalities that may occur as a result of rheumatic damage.*

support than expected from the basic scheme of normality (Fig. 3C and D).

Posterior leaflet

Deficient chordal support for the posterior leaflet was seen only among the 40 cases with a mitral valve deformity. It should be noted that the number of scallops varied considerably, since only 30 of the 40 specimens showed a tri-scalloped posterior leaflet. Of the remaining 10 specimens, eight showed four scallops while two specimens had a total of five scallops. However, a 'middle' scallop could always be identified because of a mutual chordal support derived from both papillary muscle groups. For clarity all leaflet tissues bordering the middle scallop will be grouped together as either the 'postero-medial commissural scallop' or the 'anterolateral commissural scallop', according to the terminology of Ranganathan *et al.* (1970). Abnormalities of cleft chordae will not be classified separately.

Deficient chordae were present in 36 instances, affecting only the middle scallop in 15 instances, only the posteromedial commissural scallop in two cases, and affecting both scallops at the same time in 19 hearts. The anterolateral commissural scallop was not involved in any of these specimens. In all instances ballooning was present, while in two hearts additional prolapse was identified. The latter deformity affected the middle scallop in both cases.

Three major forms of chordal aberration were identified. The first variety was mainly characterised by an overall irregular arrangement of chordae, which affected both their mode of origin as well as their insertion. This irregular arrangement was frequently associated with an underlying posteromedial papillary muscle group of a 'scattered' type with multiple small heads with muscular or fibrous bridges between them. Most chordae originated in a rather haphazard fashion from this intricate composition, while others originated from the posteroinferior free wall of the left ventricle (Fig. 4). Twenty-five of the 36 specimens with deficient chordae showed this architecture.

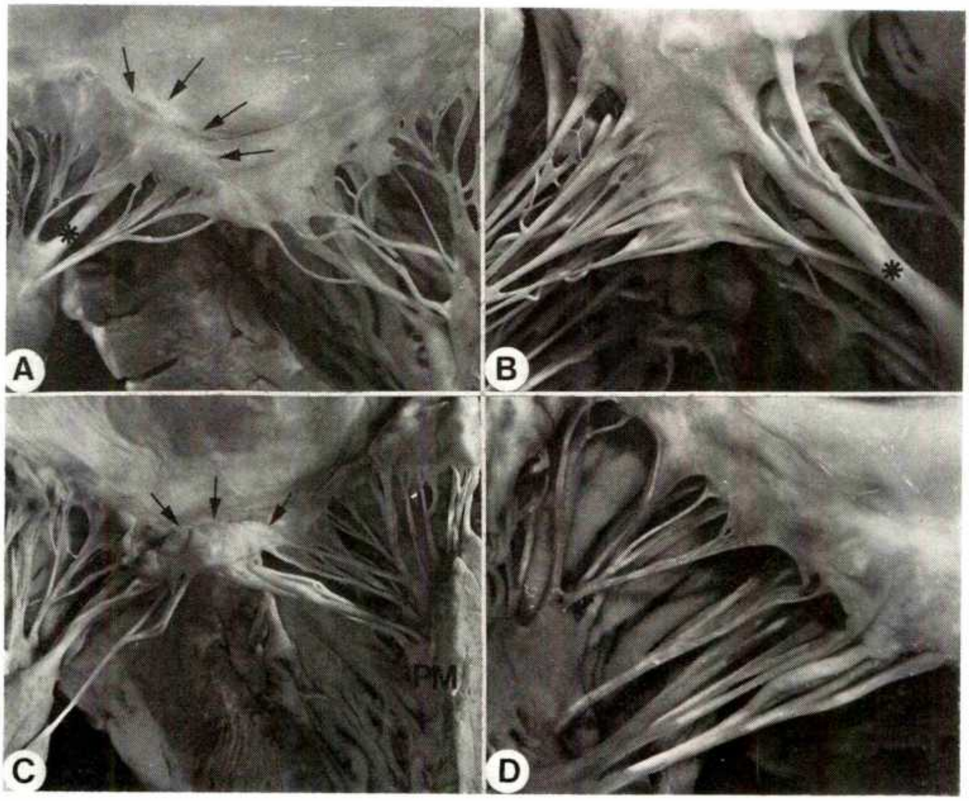

Fig. 3 *Examples of deficient rough zone chordae for the anterior leaflet.* (A) *A thickened strut chorda* (asterisk) *for the lateral half of the anterior leaflet, while the remaining rough zone chordae insert into the free margin, leaving the area neighbouring the insertion of the strut chorda relatively unsupported. The part of the leaflet so affected shows mild ballooning* (arrows). *Note the irregular chordal branching pattern for the medial half of this leaflet.* (B) *The undersurface of the anterior leaflet in another specimen. Again a thickened strut chorda* (asterisk) *is present, but the immediate surroundings are devoid of chordal insertions. There is an upward bulge of the leaflet in this region.* (C) *A bundle of rough zone chordae derived from the posteromedial papillary muscle group (PM) which insert into the free margin of the medial half of the anterior leaflet, leaving the more basal aspect unsupported. A ballooning deformity is present at that site* (arrows). *An irregular chordal distribution pattern is present also for the lateral half of this leaflet.* (D) *A similar situation, in greater detail, for the lateral half of the anterior leaflet. Note that both chordae and leaflet at that site are thickened.*

A second form of deficient chordae was characterised by pillar type papillary muscle groups, with most chordae originating from the tips. Those for the support of the 'middle scallops' were long and slender and inserted close to the free margin of the leaflets, lacking the typical distribution pattern of rough zone chordae. This arrangement was present in seven hearts, and included one of the cases having necropsy evidence of prolapse (Fig. 4B).

A third major form was characterised by the presence of a single, 'isolated' long chorda, originating as a separate structure from the posteroinferior free wall of the left ventricle. This chorda then inserted into the overlying scallop, not accompanied by other chordae for additional support. This peculiar anatomy was encountered in four specimens and in each of these the anomaly involved the middle scallop. One of the two specimens having valve prolapse presented this type of chordal arrangement (Fig. 4C and D).

Discussion

The intricate architecture of the mitral valve apparatus, in which a delicate and co-ordinated interaction of various anatomical components is a necessity for proper function, is well recognised (Perloff and Roberts, 1972). As a consequence,

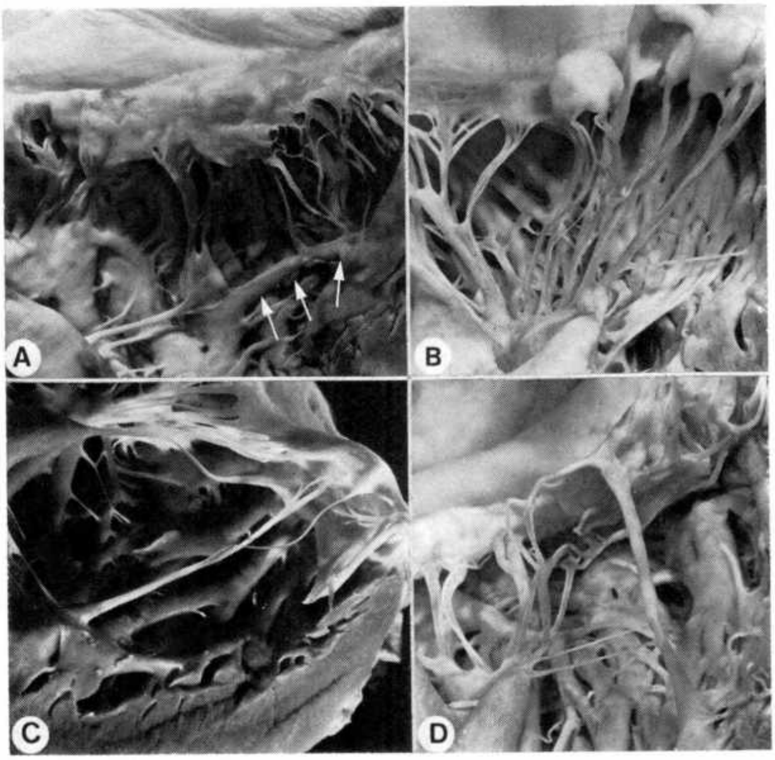

Fig. 4 *Examples of deficient rough zone chordae for the posterior leaflet.* (A) *An overall irregular distribution pattern of chordae in the presence of a multiheaded, tethered posteromedial papillary muscle group. Chordae for the posterior leaflet do in part originate from a muscular 'bridge'* (arrows) *that attaches to the anterolateral papillary muscle group.* (B) *Attenuated chordae that insert into free margin of the middle scallop, leaving the basal aspect of the leaflet without any chordal support. This is one of the two hearts in which prolapse was present.* (C) *The middle scallop of the posterior leaflets seen from the apex of the left ventricle upwards. There is a long chorda which originates as a separate structure and inserts into the rough zone area of the middle scallop, but without much support from neighbouring chordae. Pronounced ballooning is associated with this arrangement.* (D) *A similar situation in which an 'isolated' chorda inserts into the middle scallop, while a vast area of that leaflet is unsupported. This is the second heart in the series where prolapse was identified.*

there is an increasing awareness that a multitude of different disease processes, by interfering with such a co-ordinate action, may act through a final common pathway and result in mitral regurgitation. Papillary muscle dysfunction can be regarded as one such example (Cheng, 1969; Shelburne *et al.*, 1969; Perloff and Roberts, 1972). A similar awareness is growing regarding the syndrome of mitral valve prolapse. The floppy valve, defined as expansion of the mitral cusp area with elongation of chordae, is considered a major cause of this syndrome, with weakness of the central cord of the valve leaflet as the essential lesion (Davies *et al.*, 1978). Since valve leaflets so affected almost always show mucoid changes in the central connective tissue core, it has been proposed that this abnormality constitutes the essential lesion (Jeresaty, 1973, 1975; Davies *et al.*, 1978). However, mitral valve prolapse has been documented under quite different clinical circumstances, though most of these in some way or other interfere with a co-ordinated interaction of the anatomical 'building blocks' of the mitral valve apparatus (Barlow *et al.*, 1968; Perloff and Roberts, 1972; Bulkley and Roberts, 1975). There is a tendency, therefore, no longer to regard mitral valve prolapse as an entity in itself, but rather as an expression of a number of potential causes (Nutter *et al.*, 1975; Aranda *et al.*, 1976; Devereux *et al.*, 1976; Lesch, 1976). Among those causes a disproportion in size between the mitral valve and the left ventricular cavity has been suggested as a potential mechanism (Jeresaty, 1971; Criley and

Kissel, 1975; Cheng, 1976). Perloff and Roberts (1972), in their excellent display of the functional anatomy of the mitral valve apparatus, also mention the possibility that ectopically inserted chordae may contribute to mitral regurgitation, referring to a report by Levy and Edwards (1962) on the occurrence of ectopic ventricular chordal attachments as a cause of impaired valve function. These suppositions are of considerable interest because they introduce a concept of individual anatomical variations, themselves not necessarily *ab*normal, which underlie a functional disorder. Such a concept is appealing, not least because echocardiographic studies have disclosed a considerable variation in the occurrence and duration of mitral valve prolapse (Higgins *et al.*, 1976) and a surprisingly high prevalence among apparently healthy individuals (Markiewicz *et al.*, 1976; Procacci *et al.*, 1976). One may indeed wonder whether these sophisticated techniques, rather than showing overt disease, do not also record individual variations in anatomy, a proposition also favoured by Markiewicz and associates (1976) when discussing their own figures.

It is of interest, therefore, that so little attention has been given to the variability of the mitral valve apparatus. In a recent work on the normal anatomy of the mitral valve, concerning the build of leaflets and chordae tendineae, it is mentioned that aberrations from a 'basic scheme of normality' do occur (Lam *et al.*, 1970; Ranganathan *et al.*, 1970). In fact, these investigators mentioned that 'atypical' chordae were present in 39 of the 50 hearts studied. However, in approximately 60 per cent of these instances the deficient branching pattern of these chordae was compensated by an overlap from neighbouring chordae, a percentage that none the less left approximately 12 out of their 50 hearts with some sort of deficient local support for part of the valve leaflets. If one considers the fact that the mitral valve sustains considerable pressures for a prolonged time, one may perhaps speculate on the effects of an irregular distribution of chordal support on leaflets. In particular, it is already known that atrioventricular valves have a profound tendency to develop distinct upward bulges of the interchordal leaflet tissues with increasing age of the patient and in conditions accompanied by a prolonged rise in intraventricular pressures. This phenomenon has been termed 'hooding'. Indeed, Oka and Angrist (1961) have suggested that valve deformities, similar to the ones we have defined as 'ballooning deformities', result from ageing. Study of the core of the leaflets under those conditions will reveal an increase in mucopolysaccharides, probably an expression of tissue injury. Moreover, Pomerance (1969) has shown that the incidence of such deformities in a random necropsy series was encountered much more frequently in patients over 50 years of age than in younger individuals. This is not surprising if one is willing to accept that 'deficient chordae' may be present among valves which otherwise 'look normal'. If the anatomy is such that the interchordal areas widen, for instance because of a deficiency in the pattern of chordal branching, valve deformities can be expected with time. One could then also speculate whether this train of events might lead to a valve cusp with a weakened central core, expansion of the cusp area, and elongation of chordae: in other words, are some 'floppy valves' actually the end result of primary deficient chordal support?

This study has shown that pronounced differences occurred between a group of hearts designated as 'normal' and a group having a valve deformity. Among 100 'normal' hearts we found 39 specimens with a varation within the basic scheme of normality proposed by Lam *et al.* (1970) and Ranganathan *et al.* (1970). We also found that most of the variations in the present series had no deleterious effect on leaflet support because of overlap from neighbouring chordae. In this series of 'normal' hearts, only eight showed a 'deficient chorda' defined as a chorda with a non-compensated atypical branching pattern. However, it should be pointed out that this series of 'normal' hearts was selected on the basis of *not* exhibiting a valve leaflet deformity when observed in the closed state from the left atrial cavity. Hearts *with* such a deformity were included in a separate group and the incidence of deficient chordae was compared with that in the group of normal hearts. The results disclose that deficient chordae were detected among 36 of the 40 mitral valves showing a leaflet deformity. In all instances the area of the leaflet showing the deformity corresponded with the site of the deficient chorda. These findings, therefore, suggest that 'minor' variations in architecture of the chordal apparatus may leave some parts of the leaflets less well supported than others, a phenomenon which could then result in a deformity of the leaflet at that particular site. These abnormalities showed a definite tendency to occur at the site of the posteromedial commissure and related parts of the posterior leaflet, including the middle scallop, in contrast to the anterolateral parts of the valve apparatus which were less frequently affected. This observation is particularly valid when one is dealing with a 'forme frust' of a developmental anomaly, since the posteromedial papillary muscle complex was often intricately related to the chordal anomalies observed. The middle scallop in some of these hearts was reminiscent of a sort of 'watershed area', showing chordae from both papillary muscle groups inserting in the lateral free margin of the scallop, leaving the middle part less well supported. In other specimens the middle part was sustained only by a single 'strut-like' chorda, leaving a large area of the middle scallop without sufficient support; in both specimens with prolapse the middle scallop was involved. One case had a preponderance of chordal insertions among the lateral free margins, while the second case showed the 'isolated' chordal variety. It should be re-emphasised that in both instances valve prolapse was defined from the necropsy state. Regrettably, there were no relevant clinical data on the functional state of the mitral valve, since one patient died in a traffic accident, while the other patient was seen clinically at the end-stage of a malignancy.

The present observations lead to the following assumptions. Firstly, they may provide an anatomical substrate for disharmonious valve motions observed with echocardiographic techniques, suggesting that the high frequency of valve prolapse observed among apparently healthy individuals (Markiewicz *et al.*, 1976; Procacci *et al.*, 1976) reflect a spectrum of normality, rather than abnormalities of the valve itself. Similarly, the presence of deficiencies in chordal distribution may render a valve vulnerable not only to sustained high pressures but also to various conditions which may affect different components of the mitral valve apparatus. Weakening of the central core of the leaflet may act as a 'final common pathway' to a process of chronic injury, and some cases of 'floppy valve' may fit within this category.

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Oximetric detection of intracardiac left-to-right shunts[1]

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SUMMARY To assess prevailing guidelines for the oximetric detection of intracardiac left-to-right shunts, we examined the variability of right heart oxygen saturation step-ups in 1121 catheterisations in children with aortic and pulmonary stenosis, who were studied as part of the joint study of the natural history of congenital heart defects.

It is estimated that in the absence of intracardiac shunting, a step-up of more than 5·9 per cent between the superior vena cava and the pulmonary artery, 3·5 per cent between the right atrium and the pulmonary artery, and 3·6 per cent between the right ventricle and pulmonary artery, occurs 5 per cent of the time. By extrapolation from a 'normal' distribution, a step-up of 8·7 per cent between the superior vena cava and pulmonary artery, 5·6 per cent between the right atrium and pulmonary artery, and 5·2 per cent between the right ventricle and the pulmonary artery would occur 1 per cent of the time in the absence of intracardiac shunting. Assuming a normal haemoglobin concentration of 15 g/dl, the 1 per cent false positive rate corresponds to a step-up of 1·7 volumes per cent from the superior vena cava to the pulmonary artery, 1·1 volumes per cent from the right atrium to the pulmonary artery, and 1·0 volumes per cent from the right ventricle to the pulmonary artery.

These data provide guidelines for the detection of abnormal shunts, but other independent methods such as indicator dilution or angiography should be employed in borderline situations.

Cardiac catheterisation has been used to show the haemodynamic consequences of congenital heart disease since 1945 (Brannon *et al.*, 1945). It was soon recognised that left-to-right intracardiac shunting could be shown by an increase in the oxygen content in the right heart chambers, but it was also recognised that variations in oxygen content occurred even in the absence of shunting, because of incomplete mixing of the various venous streams as well as measurement errors (Brannon *et al.*, 1945; Cournand *et al.*, 1945; Baldwin *et al.*, 1946). Quantification of the normal variation became important to determine criteria for the recognition of intracardiac shunting. Dexter *et al.* (1947) in 28 patients, Barratt-Boyes and Wood (1957) in 26 patients, and Grayzel and Jameson (1963) in 63 patients studied this normal variation, but the numbers of subjects were small, the earlier methods of measuring oxygen saturation have been replaced by newer techniques, and most of their data were obtained in adults rather than in children in whom congenital heart disease is more common. Nevertheless, on the basis of these data, standards were established for the normal variability of right heart saturations and content, and have been employed extensively in the detection of intracardiac left-to-right shunting (Dalen, 1974; Jarmakani, 1977; Yang *et al.*, 1978).

In the joint study of congenital heart defects recently published (Nadas *et al.*, 1977), cardiac catheterisations were performed on over a thousand children and young adults without cardiac shunts. We have analysed these data to determine the normal range of differences in saturations in the right heart in the absence of shunts, and to define the false-positive rates for various oximetric criteria for intercardiac left-to-right shunts.

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Subjects and methods

The joint study of congenital heart defects was concerned with three lesions, aortic stenosis, pulmonary stenosis, and ventricular septal defect, from six institutions. Details of aims, results, and conclusions of the study have been published previously (Nadas *et al.*, 1977). For this report we have used the catheterisation data from children or young adults over 2 years and up to 21 years of age with aortic stenosis or pulmonary stenosis. Only investigations performed between 1 July 1966 and the conclusion of the study in mid-1973 were considered. These included the final catheterisation in the retrospective group and the initial and final catheterisations in the prospective group. A total of 1121 such catheterisations in 824 patients was available for analysis, 623 catheterisations in children with aortic stenosis and 498 in children with pulmonary stenosis.

Intracardiac left-to-right shunting was excluded by repeated clinical examination over four to eight years in all patients and at catheterisation by indicator dilution curves (green dye or fibreoptic) or angiocardiography in most. Patients with pulmonary stenosis with a gradient of more than 50 mmHg between the right ventricle and pulmonary artery were excluded because of the possibility of intracardiac right-to-left shunting in such patients.

All patients were sedated with Demerol compound (pethidine hydrochloride 25 mg/ml, promethazine hydrochloride 6·25 mg/ml, or chlorpromazine 6·25 mg/ml) in a dose of 1 ml/20 lb (1 ml/9 kg) with a maximum of 2 ml. If additional sedation was needed, pethidine hydrochloride (1 mg/kg) or chloral hydrate (30 mg/kg oral) was used. Blood samples were obtained from the pulmonary artery (PA) (branch or main), right ventricle (RV) (outflow or body), right atrium (RA) (mid-lateral), and superior vena cava (SVC) in rapid succession before indicator-dilution study or angiography. The oxygen saturation was measured by reflection oximeter or transmission spectrophotometer, periodically checked against saturations derived from PO_2 measured with a Clark electrode, calibrated using known oxygen concentrations.

Although some variations in technique were inevitable since studies were done by scores of individuals in six centres over a seven-year period, an attempt was made to standardise the order and timing of samples; work sheets were supplied to each laboratory to provide for primary recording of the data (Nadas *et al.*, 1977).

Although in most previous studies oxygen saturation or content has been compared between adjacent chambers (SVC-RA, RA-RV, and RV-PA) we compared the saturations in the individual right heart chambers with that in the pulmonary artery sample, since the latter is widely accepted to be the most completely mixed and therefore most representative sample in the absence of left-to-right shunting (Barratt-Boyes and Wood, 1957). The superior vena cava, right atrial, and right ventricular saturations were subtracted from the pulmonary artery saturation to obtain the respective percentage step-ups (which had a negative value if SVC, RA, or RV exceeded PA). Some of the reports were incomplete, with no saturation values for some of the sites. To determine whether the level of mixed venous saturation affected the variability, the data were stratified according to mixed venous saturation computed by averaging the PA saturation with the SVC, RA, or RV saturation, whichever was involved in the difference under study.

Data were extracted from the master tape and means and various centiles were calculated. Since in the range of interest the distribution followed a Gaussian pattern (data available on request), the extreme values were extrapolated from the measured 70th and 95th centile values using arithmetic normal graph paper.

Results

The cumulative distribution of the oxygen saturation difference between PA and SVC, PA and RA, and PA and RV, in the absence of intracardiac shunt, is shown in the Fig. On average the SVC and RV saturations closely approximated that in the PA, but the RA saturation was, on the average,

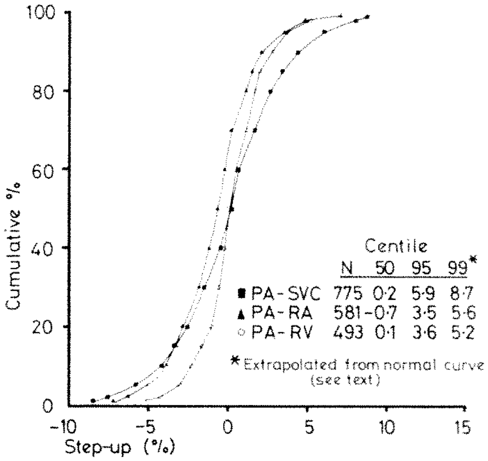

Fig. *Cumulative distribution of the differences in the oxygen saturation between the pulmonary artery (PA) and superior vena cava (SVC), right atrium (RA) and right ventricle (RV).*

Table *False positive rate for various saturation step-up criteria*

	% Step-up *3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Superior vena cava to pulmonary artery	17	12	8	5	3	1·6	0·6	0·4
Right atrium to pulmonary artery	7	4	2	0·4	0·3	0·1		
Right ventricle to pulmonary artery	9	4	1·3	0·4	0·1			

0·7 per cent higher than the PA. The PA-SVC differences had the most scatter and the PA-RV differences the least variation, though when positive differences alone were considered, the distributions of the PA-RA and PA-RV differences were quite similar. The 95th centile values for PA-SVC, PA-RA, and PA-RV were 5·9, 3·5, and 3·6 per cent, respectively. The 99th centile values, obtained by extrapolation from the Gaussian distribution, were 8·7 per cent for the PA-SVC, 5·6 per cent for the PA-RA, and 5·2 per cent for PA-RV difference. Thus, in the absence of intracardiac shunting, differences larger than these are estimated to occur in less than 1 per cent of all catheterisations.

Oxygen content was not analysed but if one assumes a normal oxygen capacity of 20·0 volumes per cent corresponding to a haemoglobin of 15 g/100 ml, the 99th centile values correspond to differences of about 1·7 volume per cent between PA and SVC, 1·1 volume per cent between PA and RA, and 1·0 volume per cent between PA and RV.

The false positive rate, that is the proportion of cases in which a shunt is thought to be present when none in fact exists, at different step-ups between PA and SVC, PA and RA, and PA and RV are illustrated in the Table. If a false positive rate of 5 per cent is accepted, shunt criteria would be differences of 6 per cent between PA and SVC, 4 per cent between PA and RA, and 4 per cent between PA and RV. Stricter criteria, with a false positive rate of 1 per cent, would be differences of 9, 6, and 6 per cent, respectively.

When the data were stratified by the mean level of the two venous saturations (less than 70%, 70 to 74%, 75 to 79%, 80 to 84%, and greater than 84%) no significant trend was found in the PA-SVC, PA-RA, or PA-RV distribution.

The distributions were similar in the patients with aortic and in those with pulmonary stenosis.

Discussion

The present data suggest that a step-up of 9 per cent from SVC to PA, 6 per cent from RA to PA, and 6 per cent from RV to PA occurs in less than 1 per cent of all catheterisations in the absence of a left-to-right shunt. This agrees well with data published earlier.

Most of the early publications were concerned with oxygen content measured by the method of Van Slyke and Neill, 1924. In 22 'normal' patients in whom atrial and ventricular samples were obtained in rapid succession, Cournand *et al.* (1945) found that the RV-RA difference ranged from −1·2 to 0·6 volumes per cent. Dexter *et al.* (1947) measured oxygen content in 13 patients without heart disease and 15 patients with a wide variety of diseases (including a few with congenital heart disease) and found a maximum step-up in oxygen content of 1·9 volumes per cent from SVC to RA, 0·9 volumes per cent from RA to RV, and 0·5 volumes per cent from RV to PA. Interestingly, these data have remained the basis of criteria for the presence of left-to-right shunt (Dalen, 1974; Yang *et al.*, 1978) for over 30 years.

Rudolph and Cayler (1958) advocated criteria based on the use of oxygen saturation rather than oxygen content for the recognition of left-to-right shunts, since saturation data are independent of haemoglobin concentration and thus unaffected by anaemia or polycythaemia. In the normal range of oxygen capacity (17·7 to 21·6 volume %) (Wood, 1949) the differences are not great, however. Barratt-Boyes and Wood (1957) studied oxygen saturations in 26 normal subjects and found that saturation differences between paired samples obtained in rapid succession had a standard deviation of 3·0 per cent for SVC and RA (82 sample pairs in 26 subjects), 2·9 per cent for RA and RV (44 sample pairs in 24 subjects), and 1·7 per cent for RV and PA (23 sample pairs in 18 subjects). The variability could be reduced to SD of 2·3 per cent, 1·6 per cent, and 1·2 per cent if two or more samples were taken from each site. From these data they concluded that the presence of a left-to-right shunt could be deduced when the RA saturation exceeds the SVC saturation on two paired samples by more than 8 per cent, when the RV saturation exceeds the RA saturation by 3 per cent, or when the PA saturation exceeds the RV saturation by more than 2 per cent, or from an extrapolation of their data, 9, 6, or 4 per cent respectively on single paired samples.

Rudolph and Cayler (1958) took the view that an increase in saturation of 10 per cent from SVC to RA, 7 per cent from RA to RV, and 5 per cent from RV to PA were the minimum changes indicative of a left-to-right shunt on a single set of paired samples. This was based on experience with cardiac catheterisation in over 1250 children with all types of congenital and acquired heart disease, but no further information about the basis of these conclusions was made available and no systemic study seems to have been done. Our data indicate that use of Rudolph and Cayler's criteria would be associated with a false positive rate of 0·4 per cent for PA-SVC, 0·3 per cent for PA-RA, and 1·3 per cent for PA-RV.

It should be recognised that an observed step-up less than the diagnostic cut-off value does not indicate absence of an intracardiac shunt. Even an appreciable shunt may fail to produce a step-up higher than which can be found, though rarely, in the absence of shunt. Our data provide no criteria for the exclusion of a shunt.

We have not used oxygen saturation criteria for patient inclusion or exclusion in this study since such criteria would bias the study. It is possible that a few patients with a small shunt have been included, and some patients without a shunt may have been excluded on the basis of a large rise in oxygen saturation between SVC and PA. Evidence of associated cardiac disease was, however, diligently sought, and, if found, called for exclusion from the natural history study. All patients had yearly clinical examinations and at least one and, in more than two-thirds of the cases, two cardiac catheterisations including angiocardiography and dye dilution studies. While it is conceivable that some intracardiac shunts have been missed, the number must be quite small. Likewise, the number of patients who were excluded from the natural history study, because of the erroneous belief that a shunt was present, must also be small. Most of the patients with aortic stenosis or pulmonary stenosis in whom an associated shunt was suspected had additional tests such as dye-dilution studies or angiocardiography, and were included when these failed to confirm the presence of a shunt. If patients with large step-ups had been excluded, asymmetry of the step-up distribution would have been seen with partial truncation at the top as a result of removal of these patients; no such asymmetry is apparent in the Fig.

These are three probable reasons for the observed variation between SVC, RA, RV, and PA saturations in the absence of a left-to-right shunt: measurement error in the oxygen analysis, changes in the physiological state of the patient during the sampling run, and incomplete mixing of the venous streams in the right heart. The 'gold standard' for oxygen analysis has been the manometric method of Van Slyke and Neill (1924). This technique, however, is cumbersome and time consuming and has been replaced almost completely by direct measurements of oxygen saturation by spectrophotometer, reflection oximeter, or indirect measurements from pH and Po_2 using Severinghaus oxygen dissociation curves. These three methods have been shown to correlate very well (Lopez-Majano *et al.*, 1971) and, though some measurement variability is inevitable, it can probably be reduced to no more than 1 per cent if the oximeters are calibrated and standardised regularly (Barrett-Boyes and Wood, 1957). Sources of error related to the physiological state of the patient include changes in cardiac output, oxygen consumption, or ventilation while the samples are being obtained. These errors are minimised if the samples are obtained in rapid succession with the patient in a steady state. Incomplete mixing resulting from laminar flow probably represents the major source of error. Inferior vena caval blood is so poorly mixed that many observers no longer use this sample at all (Rudolph and Cayler, 1958). It is widely agreed that the pulmonary arterial sample is the best mixed because turbulence in the right ventricle destroys laminar flow. Better mixing can presumably be achieved in the right atrium by sampling in the mid-lateral position, away from the coronary sinus return, and in the right ventricle by sampling from the outflow tract, but evidence for this is lacking.

The magnitude of the variability caused by poor mixing cannot be separated from that caused by the other two factors in our study. Samples from the SVC and PA were more widely separated in the time than the RV and RA samples, thus allowing possible changes in the physiological state of the patients to confuse the results. The data from Barratt-Boyes and Wood (1957), however, where SVC and RA, RA and RV, and RV and PA samples were obtained at the same intervals, show, as did our data, least variability in the more distal samples. This suggests that the lesser variability in the distal samples in our study is indeed the result of better mixing rather than of changes in the physiological states of the patients. It is not possible, however, from our study to say whether the RV-PA differences resulted from incomplete mixing or measurement error.

Our data contribute to the understanding of the magnitude of the variability in oxygen saturation step-ups in the absence of an intracardiac left-to-right shunt, and provide guidelines for the detection of these shunts. The 99 centile levels (8% for shunt at atrial level, 6% for shunt at ventricular level, and 5% for aortopulmonary shunt) are only guidelines, however, and in borderline situations other independent methods such as indicator dilution curves or angiocardiography should be employed.

We are grateful to the 27 investigators and their staffs at the participating centres of the joint study on the natural history of congenital heart defects for allowing us to use their data. We also thank Mr John Rees for help in data extraction and analysis.

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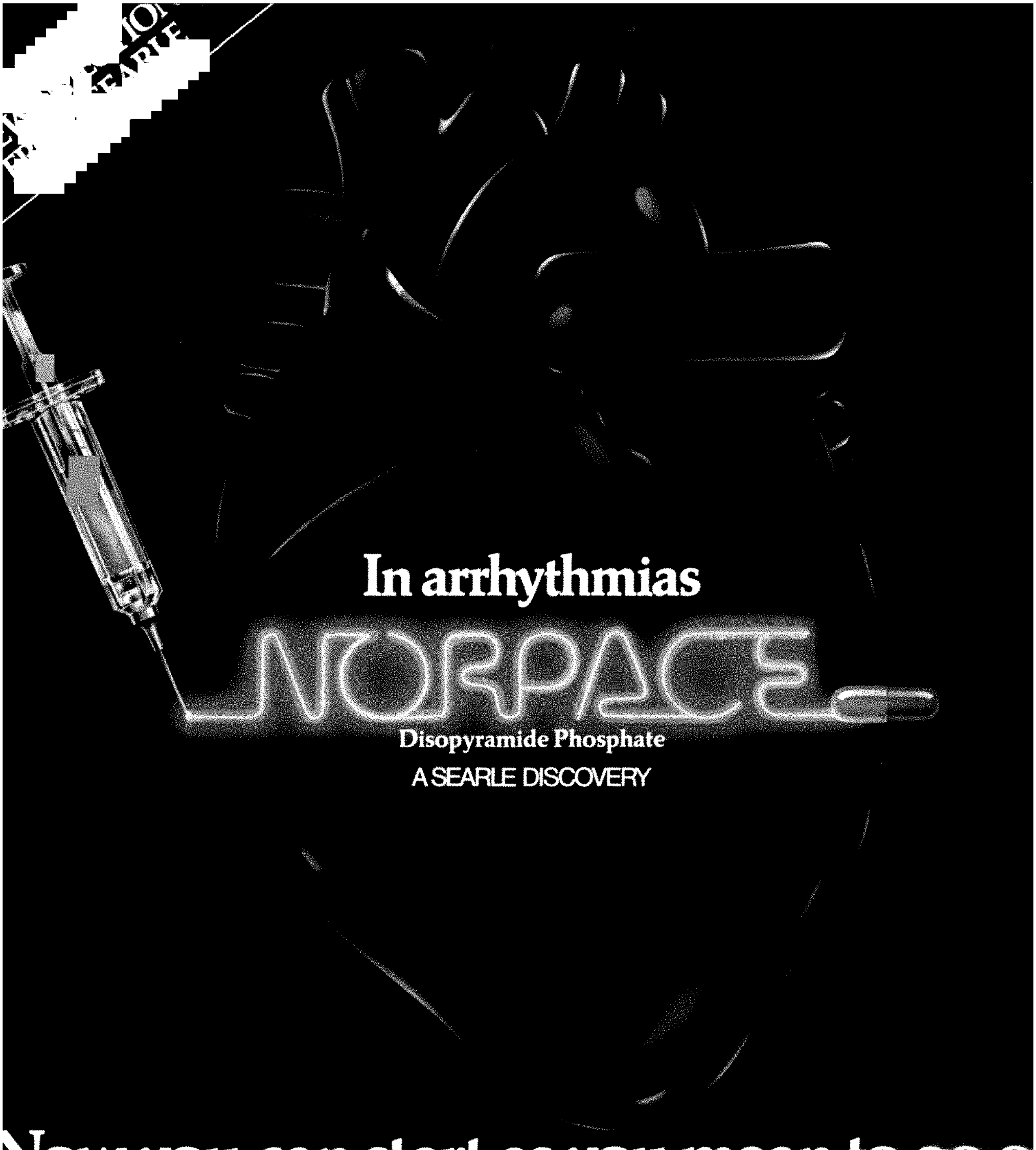

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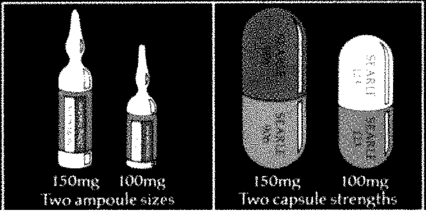

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British Heart Journal, 1979, **42**, 695–702

Factors responsible for normal splitting of first heart sound

High-speed echophonocardiographic study of valve movement

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SUMMARY Echocardiographic studies have confirmed that normal splitting of the first heart sound is a result of mitral valve closure preceding tricuspid valve closure. This fits in with contraction of the left ventricle before the right, but the width of splitting is usually greater than would be expected from the known ventricular asynchrony. The importance of atrial systole, which initiates closure of the atrioventricular valves, has not been considered. In this study of 67 normal subjects, high-speed echophonocardiograms were recorded and the timing of mitral and tricuspid valve closure was related to the PR interval and the beginning of left and right ventricular ejection.

The timing of mitral valve closure was strongly influenced by the PR interval; in patients with a long PR interval the valve leaflets were nearly apposed by atrial systole and closure was completed early after the Q wave on the electrocardiogram, while with a short PR interval the leaflets were still widely separated at the time of ventricular activation and closure was completed later. The timing of tricuspid closure was affected similarly but less strongly, and even when the PR interval was so long that mitral closure was complete before the onset of left ventricular systole, tricuspid closure occurred up to 48 ms later. The mean interval between mitral and tricuspid closure was 34 ms. Thus mitral closure was effected nearer the onset of left ventricular systole than was tricuspid closure in relation to the onset of right ventricular systole, and this accounts for the surprising width of splitting of the first sound. Variations in splitting of the first sound were mainly the result of variations in the timing of tricuspid rather than of mitral closure. When tricuspid closure was delayed, so was pulmonary valve opening, suggesting that the cause was delay in the onset of right ventricular systole or a slower rate of pressure development in the right ventricle.

It was postulated by Dock (1933) that the major components of the first heart sound were the result of tensing of the atrioventricular valves after the rise in ventricular pressure at the onset of systole. Simultaneous high frequency sound recordings from the apex and lower left sternal edge together with an indirect carotid pulse tracing led to the conclusion that splitting of the first sound into two components was commonly found in normal subjects, and that mitral closure preceded tricuspid (Leatham, 1954). This view has been challenged and tricuspid closure reported to be silent (Luisada *et al.,* 1974), but simultaneous echo- and phonocardiograms ('echophonocardiograms') have shown exact coincidence between the final halt of the closing mitral valve and the onset of the first major component of the first sound, and between tricuspid valve closure and the onset of the second group of high-frequency vibrations (Burggraf and Craige, 1974; Leatham and Leech, 1974; Waider and Craige, 1975). Using echophonocardiography it is possible for the first time to identify the two components with certainty, and it is therefore opportune to re-examine the factors responsible for physiological splitting of the first heart sound.

Wide splitting of the first sound in bundle-branch block and during artificial pacing results from asynchronous ventricular contraction (Wolferth and Margolies, 1935; Haber and

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Leatham, 1965; Brooks *et al.,* 1979), but obvious splitting is also found in some normal subjects and it is not known whether or not this, too, is caused by ventricular asynchrony. Since atrioventricular valve closure is initiated by atrial contraction and relaxation (Henderson and Johnson, 1912; Little *et al.,* 1954; Zaky *et al.,* 1969), the timing of the two components of the first sound is also affected by the PR interval, and this important variable factor has not been taken into account in previous studies. In the present study high-speed simultaneous recordings of the echo- and phonocardiogram were used to assess the extent to which normal splitting of the first heart sound is affected by asynchronous ventricular contraction and by the effects of left and right atrial contraction on mitral and tricuspid valve closure, respectively.

Methods

We studied 67 normal subjects. Their ages ranged from 19 to 56 (mean 32) years and there were 27 men and 40 women. The three standard bipolar limb leads of the electrocardiogram were recorded simultaneously at four times normal calibration (1 mV=4 cm) and at a paper speed of 100 mm/s. The lead showing the earliest QRS deflection was selected for recording with the echophonocardiogram.

Echocardiograms were recorded on a Smith-Kline Ekoline 20 ultrasonoscope interfaced with a Cambridge six-channel photographic recorder. The system was modified to double its echo-depth magnification and increase the maximum paper speed to 200 mm/s. These adaptations permit resolution of tissue depth to 0·5 mm and time intervals to 2·5 ms.

The four heart valves were identified by standard echocardiographic techniques. Care was taken to record the moment of closure of the mitral and tricuspid valves, this being defined as the point of apposition of the anterior and posterior leaflets. Sometimes it was not possible to demonstrate two tricuspid valve leaflets, and a definite 'shoulder' on one was accepted. The technique for demonstrating tricuspid valve closure, and the typical appearance obtained, is described in detail elsewhere (Brooks *et al.,* 1979). For the aortic valve recording, the transducer position was adjusted to show separation of the valve cusps at the onset of ventricular ejection. It is usually possible to identify only one pulmonary valve cusp (the posterior), so that the moment of *onset* of right ventricular ejection cannot be defined precisely. For this reason recordings were made which showed the full extent of its opening movement. This point is often marked by a well-defined 'shoulder' as the rapid posterior movement is arrested and the cusp begins to move slowly anteriorly; when this shoulder was not seen the point at which the cusp echoes merge with those from the posterior wall of the right ventricular outflow tract was recorded. Previous studies have shown that this point can be defined consistently with little interobserver variation (Mills *et al.,* 1975).

A high-frequency phonocardiogram with the microphone positioned to detect both major components of the first sound was recorded simultaneously with the echocardiogram. The best microphone position was usually at the lower left sternal edge, but in a number of cases a site nearer to the apex was optimal. In subjects with a single first sound the left sternal edge position was used.

All recordings were made in shallow held expiration with maximal magnification of the echo display and at 200 mm/s paper speed.

MEASUREMENTS

The PR interval was measured on the simultaneous three-lead electrocardiogram from the onset of P to the onset of QRS using the leads which gave the earliest deflections. The mean of five cycles was expressed to the nearest 5 ms. Heart rate was measured on the echophonocardiogram. The following echocardiographic intervals were determined:

(1) From the onset of the QRS complex to the earliest point of coaptation of the mitral leaflets at the moment of valve closure (Q-MC).

(2) From the onset of the QRS complex to tricuspid valve closure (Q-TC).

(3) From the onset of the QRS complex to the earliest separation of the aortic valve leaflets (Q-AO).

(4) From the onset of the QRS complex to complete opening of the pulmonary valve (Q-POm).

Measurements were made with a hair-line cursor to the nearest 0·5 mm (2·5 ms) in a minimum of five cardiac cycles and the mean value was expressed to the nearest millisecond. When the Q wave was poorly defined for a particular beat, measurements were made from the peak of the R wave and the Q to R time was added.

Fig. 1 shows echocardiograms of all four heart valves with a simultaneous electrocardiogram and phonocardiogram from a single subject to illustrate the recordings and measurements.

Statistical calculations were carried out on a Hewlett-Packard 9810A calculator using standard formulae.

Results

TIMING OF MITRAL AND TRICUSPID VALVE CLOSURE

Technically satisfactory recordings of the mitral valve were made in all 67 subjects, of the tricuspid valve in 63 subjects, and of the phonocardiogram in 58 subjects.

The mitral valve closed before the tricuspid valve in all cases. In 45 subjects there were two identi-

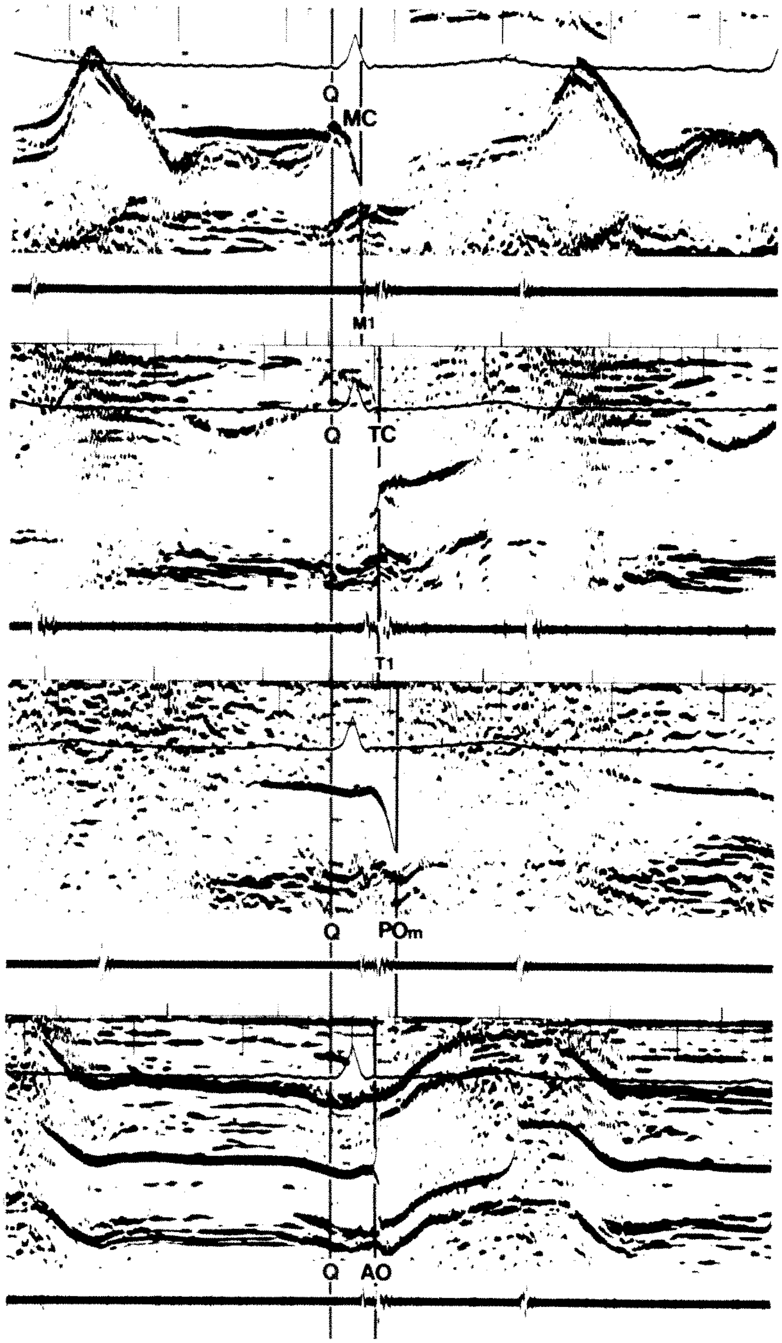

Fig. 1 *Echocardiograms of the mitral, tricuspid, pulmonary, and aortic valves recorded with a simultaneous electrocardiogram and phonocardiogram from a normal subject. MC, mitral valve closure; TC, tricuspid valve closure; AO, onset of aortic valve opening; POm, maximal opening of pulmonary valve; M1, mitral component of first heart sound; T1, tricuspid component of first heart sound. Time lines 40 ms.*

fiable high-frequency components of the first sound on the phonocardiogram; the onset of the first component (M1) coincided exactly with mitral closure on the echocardiogram and the onset of the second component (T1) coincided with tricuspid closure (Fig. 1). In seven out of the eight subjects with a single first sound its onset was synchronous with mitral closure and the tricuspid valve closed so soon afterwards that T1 was presumed to be superimposed on M1. In one individual with a PR interval of 220 ms, the mitral valve closed silently 27 ms after the Q wave; a single sound occurred 42 ms later and coincided with tricuspid valve closure (Fig. 2). In five subjects, all of whom had PR intervals of 190 ms or longer, neither M1 nor T1 could be recorded.

Mean Q-MC was 54 ms (SD 13), but the timing of mitral closure was influenced strongly by the PR interval. When the PR interval was long valve closure occurred soon after the QRS onset (short Q-MC) because of previous partial apposition of the cusps caused by atrial contraction and relaxation.

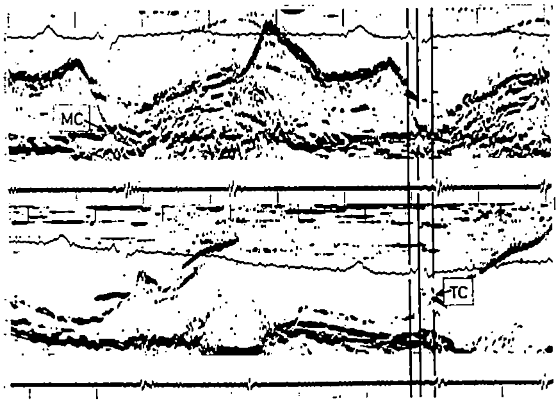

Fig. 2 *Echocardiograms of the mitral and tricuspid valves with a simultaneous phonocardiogram from a subject with a PR interval of 220 ms. The recordings have been aligned on the QRS complex of the electrocardiogram and show early, silent mitral valve closure with the single first sound occurring synchronously with tricuspid valve closure. Abbreviations as in Fig. 1.*

With short PR intervals the cusps were less closely apposed at the onset of ventricular contraction and Q-MC was long. There was a highly significant inverse linear correlation between Q-MC and PR interval (Fig. 3). The equation of the line is:

$$\text{Q-MC} = -0{\cdot}67.\ \text{PR} + 158$$

($r = -0{\cdot}72$, $P < 0{\cdot}001$).

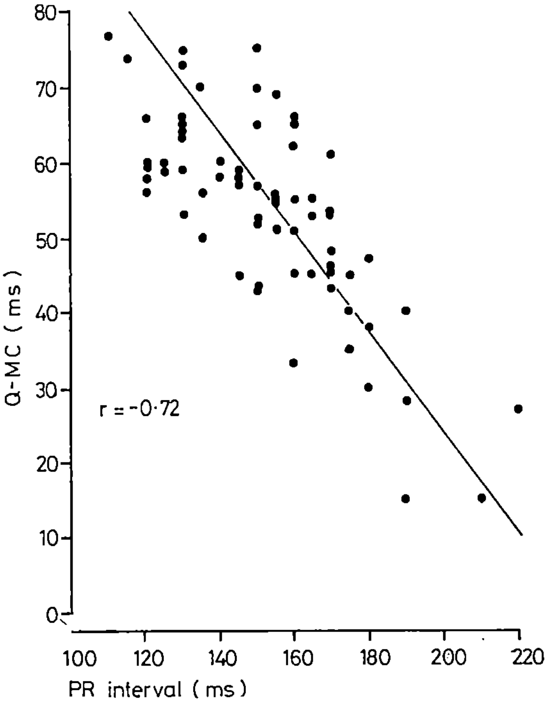

Fig. 3 *The relation between PR interval and the timing of mitral valve closure (Q-MC).*

The timing of valve closure was not significantly affected by heart rate, the correlation coefficient between Q-MC and heart rate being –0·27 and the partial correlation coefficient (keeping PR interval constant) –0·41.

The PR interval had a similar effect on the timing of tricuspid valve closure, but there was an important difference from the mitral valve. There was a highly significant correlation between Q-TC and PR interval (Fig. 4) given by the equation

$$\text{Q-TC} = -0{\cdot}45.\ \text{PR} + 155$$

($r = -0{\cdot}6$, $P < 0{\cdot}001$), but the slope of this line is significantly less steep than that of the Q-MC/PR interval relation ($P < 0{\cdot}05$). In other words, right atrial contraction and relaxation was less effective than that of the left in closing its atrioventricular valve. Like the mitral valve the timing of tricuspid closure was unaffected by heart rate.

In order to compare the timing of mitral and tricuspid valve closure between subjects with different PR intervals, Q-MC and Q-TC indices, in which the timing of valve closure is corrected to an arbitrary PR interval of 160 ms, were calculated from the regression coefficients using the equations:

Q-MC index = Q-MC + 0·67. PR - 107
Q-TC index = Q-TC + 0·45. PR - 72.

Mean Q-MC index was 48 ms (SD 10 ms) and mean Q-TC index was 84 ms (SD 13 ms).

Mean MC-TC, the interval between closure of the mitral and tricuspid valves, was 34 ms (SD 10 ms). Though the timing of mitral and tricuspid closure was affected unequally by variations in the PR interval there was no significant correlation between MC-TC and PR interval because of the wide scatter of the results. MC-TC showed no tendency to shorten at longer PR intervals. Fig. 5 shows the Q-MC and Q-TC intervals in seven subjects with PR intervals of 180 ms or longer: MC-TC ranged from 18 to 48 ms.

TIMING OF AORTIC AND PULMONARY VALVE OPENING

Satisfactory recordings of the aortic valve were made in 45 subjects and of the pulmonary valve in 47 subjects.

Mean Q-AO was 94 ms (SD 16 ms). There was no significant correlation between the timing of aortic opening and heart rate.

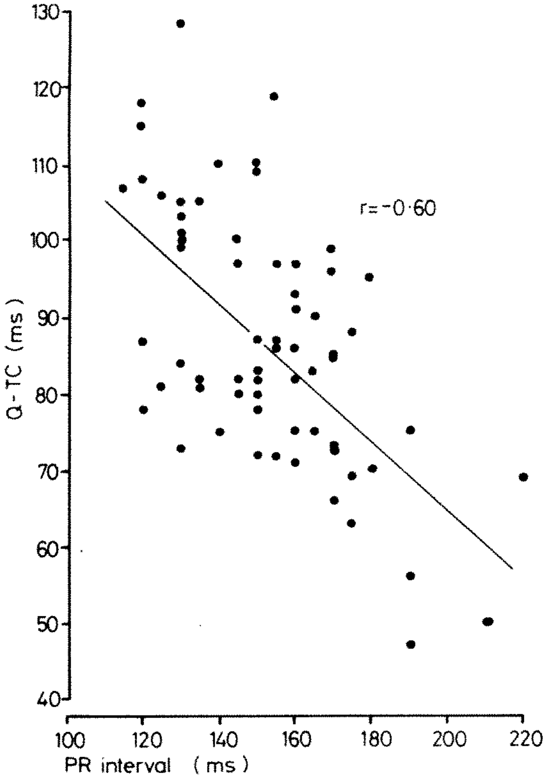

Fig. 4 *The relation between PR interval and the timing of tricuspid valve closure (Q-TC).*

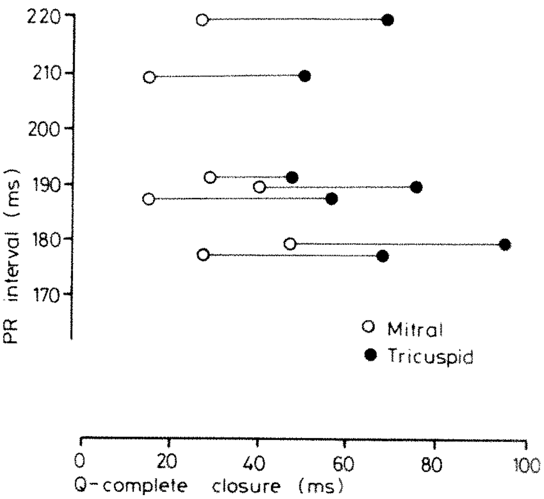

Fig. 5 *The Q-MC, Q-TC, and MC-TC intervals in seven subjects with PR intervals equal to or exceeding 180 ms.*

Mean Q-POm was 126 ms (SD 13 ms) and there was a weak ($r = -0·51$) but highly significant ($P < 0·001$) linear correlation between the timing of pulmonary valve opening and heart rate (Fig. 6). The equation of the line is:

Q-POm = -0·58 (heart rate) + 165.

To compare the timing of pulmonary opening between subjects with different heart rates Q-POm was therefore corrected to a heart rate of 60/min (Q-POm index) from the equation:

Q-POm index = Q-POm + 0·58 (heart rate) - 35.

Mean Q-POm index was 129 ms (SD 11 ms).

RELATION BETWEEN ATRIOVENTRICULAR VALVE CLOSURE AND AORTIC AND PULMONARY VALVE OPENING

There was a highly significant linear correlation between MC-TC and Q-TC index ($r=0·74$, $P < 0·001$) which is shown in Fig. 7. There was no significant correlation between MC-TC and Q-MC index.

Tricuspid valve closure, whether timed from the Q wave of the electrocardiogram (Q-TC index) or from closure of the mitral valve (MC-TC), was significantly related to the timing of pulmonary valve opening. Fig. 8 shows the correlation between Q-TC index and Q-POm index ($r=0·71$). The

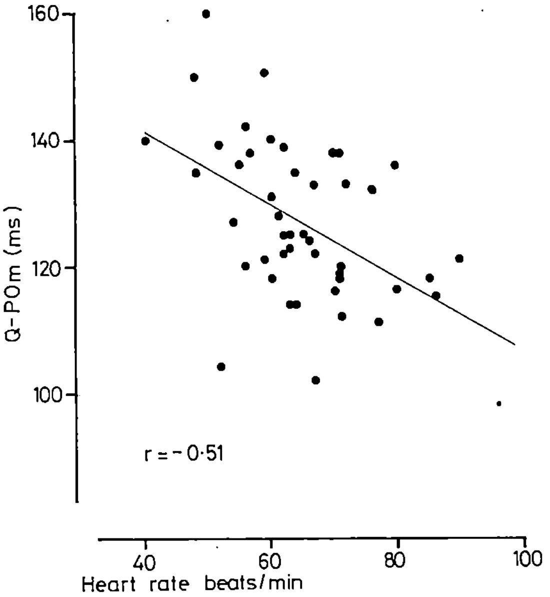

Fig. 6 *The relation between heart rate and the timing of complete opening of the pulmonary valve (Q-POm).*

correlation between MC-TC and Q-POm index was less close ($r = 0{\cdot}59$) but still highly significant ($P < 0{\cdot}001$). By contrast there was no significant correlation between the timing of mitral closure (either MC-TC or Q-MC index) and the timing of aortic opening (Q-AO).

The results are summarised in the Table.

Discussion

Previous studies on the first heart sound have been impeded by the inability to identify its two major components with certainty in all subjects. The exact coincidence of mitral and tricuspid valve closure with the corresponding sound components M1 and T1 has been established both by haemodynamic and echocardiographic techniques (Burggraf and Craige, 1974; Leatham and Leech, 1974; O'Toole *et al.,* 1976). High-speed echocardiograms recorded simultaneously with the phonocardiogram thus made it possible to study the factors determining the timing of M1 and T1 in normal subjects, since accurate measurement is possible even when the valves close nearly synchronously and the two components are merged into each other on the sound recording.

The results of the present study show that the PR interval is a major determinant of the timing of mitral and tricuspid valve closure in normal subjects. At a PR interval of 180 ms Q-MC is about 30 to 40 ms (Fig. 3). This is approximately the time between electrical depolarisation and the onset of the left ventricular pressure pulse (Braunwald *et al.,* 1956; Luisada and Cortis, 1970), and so it may be concluded that when the PR interval is longer than this the mitral valve is closed entirely by atrial contraction and relaxation. Zaky *et al.* (1969) drew similar conclusions, though Shah *et al.* (1970) and Burggraf and Craige (1974) in their studies of patients with complete atrioventricular block found evidence of presystolic valve closure only when the PR interval exceeded about 200 ms. With shorter atrioventricular conduction times mitral closure, though initiated by atrial contraction and relaxation, is completed by ventricular contraction.

The tricuspid valve, however, does not close before the onset of the right ventricular pressure pulse unless the PR interval is considerably longer than 180 ms. In the subjects with PR intervals equal to or exceeding 180 ms, tricuspid closure still followed mitral closure by an interval of up to 48 ms (Fig. 5). In one subject (Fig. 2) with a PR interval of 220 ms, the mitral valve must have closed before the beginning of left ventricular contraction since Q-MC was 27 ms and no M1 was recorded. The tricuspid valve, however, closed 42 ms later (69 ms after the Q wave) and was associated with a definite T1 on the phonocardiogram. The time between the Q wave of the electrocardiogram and the onset of

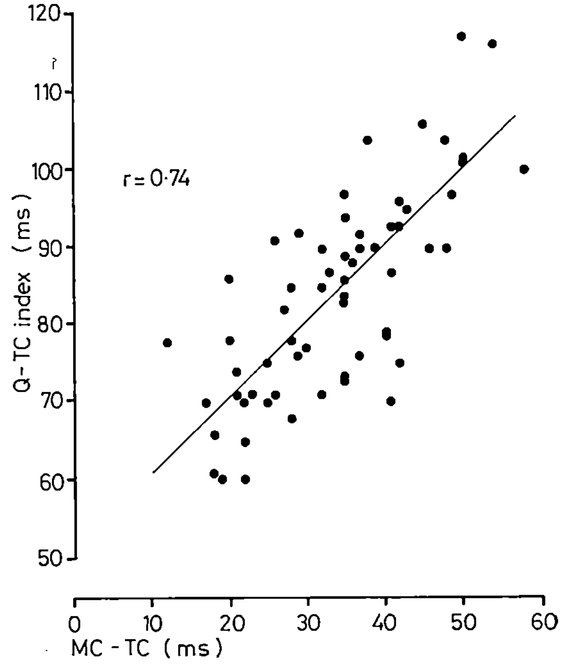

Fig. 7 *The relation between MC-TC and Q-TC index.*

the right ventricular pressure upstroke is said to be about 50 ms (Luisada and Cortis, 1970) and so it is probable that, despite the very long PR interval in this individual, tricuspid closure was completed after the onset of right ventricular contraction. These observations, together with the finding of a steeper slope of the Q-MC/PR interval relation compared with the Q-TC/PR interval relation, indicate that contraction of the right atrium has a less powerful valve-closing action than contraction of the left atrium. Since the right atrium starts to contract before the left (Braunwald *et al.,* 1956), the difference is substantial. This explains the apparent discrepancy pointed out by Luisada *et al.* (1974) that the average interval between the two components of the first sound, M1 and T1, is over 30 ms, whereas the interval between the onset of left and right ventricular contraction is less than 20 ms. It seems that over the physiological range of PR interval the mitral valve is more nearly closed when left ventricular contraction begins than is the tricuspid valve at the start of right ventricular contraction, so that the time from right ventricular contraction to tricuspid valve closure and T1 is longer than the time from left ventricular contraction to mitral valve closure and M1.

Mean MC-TC in the present study was 34 ms, but there was wide variation between subjects. The strong correlation between MC-TC and Q-TC index suggests that this variation in MC-TC (and splitting of the first sound) is mainly the result of differences in the timing of tricuspid rather than mitral valve closure. This variability in the timing of tricuspid closure has a number of possible explanations. The difference might be in the valve-closing action of right atrial contraction from one person to another, in the rate of rise of right ventricular pressure imparting a variable closing force on the valve, or in the timing of right ventricular contraction. One or both of the second two possibilities is supported by our demonstration of a correlation between the timing of tricuspid valve closure and the timing of pulmonary valve opening, since delayed pulmonary opening could reflect either delayed onset of right ventricular contraction or a slow-rising pressure upstroke, and early opening either early contraction or a rapid upstroke. Both Braunwald *et al.* (1956) and Luisada and Cortis (1970) showed that there was considerably more variation in the timing of right ventricular contraction (measured as the time from the Q wave to the start of the right ventricular pressure pulse) than in the timing of left ventricular contraction, and so we believe that it is this which is principally responsible for variations in the timing of tricuspid valve closure between one normal person and another. No significant correlation was found between the timing of mitral valve closure and aortic valve opening, and this seems to indicate that variations in timing of mitral closure and M1 are not caused primarily by differences in timing of left ventricular contraction, or the rate of pressure rise.

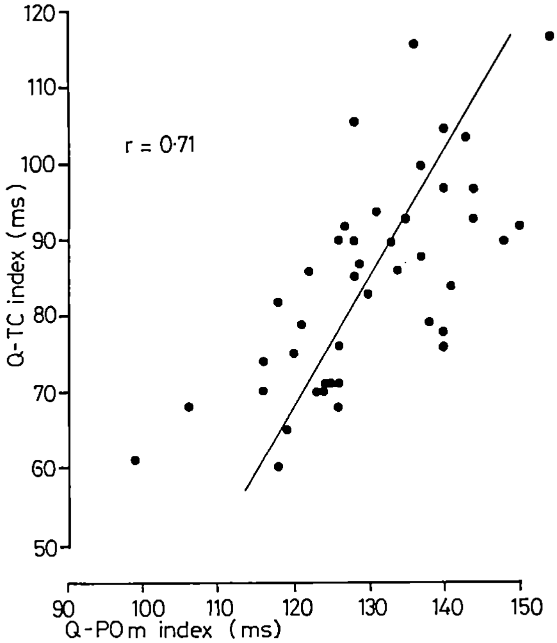

Fig. 8 *The relation between the timing of tricuspid valve closure corrected for PR interval (Q-TC index) and the timing of maximal pulmonary valve opening corrected for heart rate (Q-POm index).*

Table *Mean echocardiographic intervals*

Interval	*Mean (ms)*	*Standard deviation*	*No.*
PR	151	25	67
Q-MC	54	13	67
Q-MC index	48	10	67
Q-TC	87	17	63
Q-TC index	84	13	63
MC-TC	34	10	63
Q-AO	94	16	45
Q-POm	126	13	47
Q-POm index	129	11	47

By extrapolation from the echocardiographic findings, we have shown that normal splitting of the first heart sound, which is wider than expected from the known degree of asynchronous ventricular contraction, is determined by a difference in the effects of left and right atrial contraction on mitral and tricuspid valve closure. Variations in the timing of the tricuspid component are probably the result of variations in the timing of right ventricular activation and contraction, despite the absence of evidence of electrical delay on the electrocardiogram.

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The work described is part of a study submitted by N. B. to the University of London for the degree of Doctor of Medicine.

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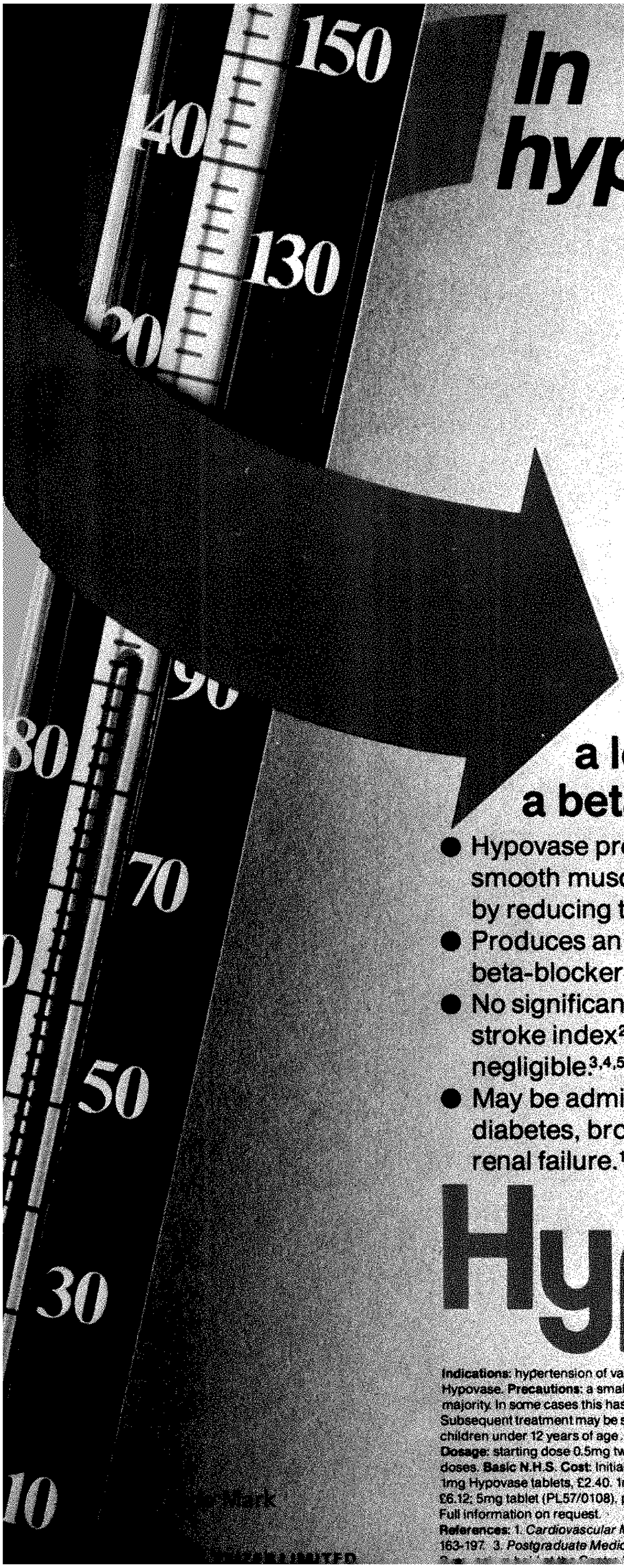

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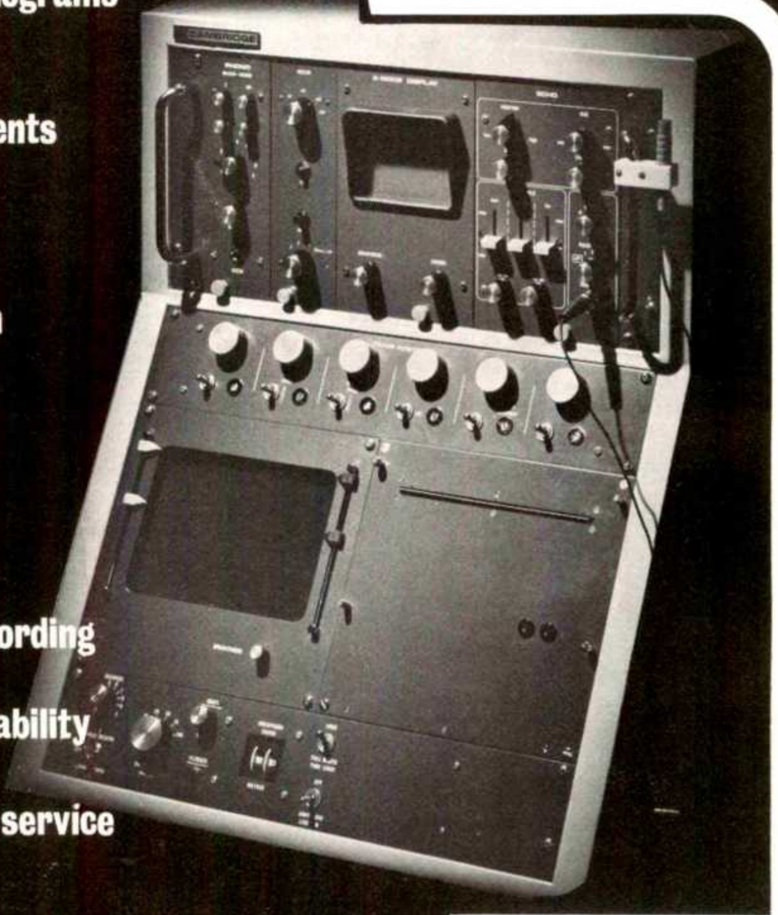

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British Heart Journal, 1979, **42**, 703–708

Current management of cardiac transplant recipients[1]

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SUMMARY Changes in the management of cardiac transplant recipients over the past 10 years have resulted in a substantial improvement in the outlook for survival. Imuran and prednisone remain the primary immunosuppressive agents, but rabbit antihuman thymocyte globulin is used initially and reinstituted during rejection.

Endomyocardial biopsy has allowed more precise diagnosis and management of rejection, and more recently immunological monitoring has been introduced to provide more frequent assessment of the host immune response.

Infection is the major cause of death, and its diagnosis and treatment is managed aggressively. Current survival figures justify the use of cardiac transplantation, by an experienced team, when other measures have been exhausted.

Cardiac transplantation was introduced as a therapeutic procedure 11 years ago. It was received with widespread initial enthusiasm and eventually was performed by 66 units throughout the world. Within three years of the clinical advent of heart transplantation, realisation of the complex challenges involved in the successful management of cardiac transplant recipients and the generally low survival rates achieved, resulted in the abandonment of the project in all but a few centres. At Stanford University Medical Center an active clinical programme in heart transplantation, initiated in 1968, has continued, however, and the level of activity has steadily increased. By January 1978, a total of 378 cardiac transplantation operations had been performed world wide and 97 patients were then surviving. One hundred and thirty-six of these patients had had their operations at Stanford, with 55 survivors. By the end of 1978 the total number of recipients at Stanford had increased to 161 patients with 67 survivors.

Postoperative management of the recipient has continued to evolve. Changes have resulted from both clinical experience and continuing laboratory research devoted entirely to the study of cardiac transplantation during the past 20 years. These have resulted in an improvement of one-year survival rates from 22 per cent in 1968 to 67 per cent in 1977 (the most recent year providing a minimum follow-up of one year). In this report we give an account of those aspects of treatment relevant to successful postoperative management of cardiac recipients.

Immunosuppression

As in the case of other solid organ allografts, indefinite immunosuppression, instituted at the time of transplantation, is required for cardiac graft acceptance. The standard immunosuppressive regimen used in our programme consists of azathioprine, corticosteroids, and antihuman thymocyte globulin produced in rabbits, administered as described below.

AZATHIOPRINE

A loading dose of azathioprine (3 to 5 mg/kg) is given before operation upon confirmation of donor availability. A daily maintenance dose is then established which is the maximum tolerated without leucopenia or thrombocytopenia (usually 1·5 to 2·0 mg/kg).

CORTICOSTEROIDS

Methylprednisolone, 500 mg, is given intravenously

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during operation, followed by 125 mg every eight hours for three doses. Then, upon resumption of oral intake, maintenance prednisone is started at a dose of 1·5 mg/kg per day. The daily dose is then tapered by decrements of 2·5 mg until a maintenance level of 1·0 mg/kg is reached; this is kept constant until approximately two months after transplantation when further gradual reduction of daily dose to 0·25 to 0·40 mg/kg is attempted. Both the rate of decrease of dose and the established maintenance dose of prednisone are determined by the state of graft acceptance.

ANTITHYMOCYTE GLOBULIN

Antihuman thymocyte globulin of rabbit origin (RATG) is administered immediately before operation and then daily for 10 to 14 days after operation in single doses of 2·5 mg/IgG per kg. Subsequently, reinstitution of individually prescribed courses of RATG is determined by the results of immunological monitoring (see below) and the occurrence of diagnosed acute rejection episodes. RATG is produced in the cardiovascular surgical laboratories, and current preparations may be administered either intramuscularly or intravenously. ATG produced in rabbits has, in our experience, had a greater immunosuppressive effect than similar heterologous antisera produced in horses and administered intravenously (Griepp *et al.*, 1977a).

Diagnosis of acute rejection episodes

With current immunosuppressive regimens only 10 per cent of patients have no episodes of acute graft rejection during the first three months after cardiac transplantation. The average frequency of acute rejection episodes during this time is one per 22 patient-days. Later, the frequency of acute rejection episodes decreases considerably (one episode per 325 patient-days after the first year). Effective postoperative management thus depends upon sensitive reliable diagnosis and successful management of impending graft rejection.

The clinical diagnosis of acute rejection is based upon signs that reflect impairment of graft function. Changes in ventricular mechanics caused by lymphocytic infiltration and interstitial oedema result in a decrease in myocardial compliance and contractility. A diastolic gallop rhythm (a third or fourth heart sound or both) appears early; signs of low cardiac output and congestive failure develop only with severe graft rejection. Chest *x*-ray films may show varying degrees of cardiomegaly or pericardial effusion. Changes in standard electrocardiograms include a generalised decrease in QRS voltage, a rightward shift of the mean frontal plane axis, atrial arrhythmias, and occasionally ischaemic ST-T changes (Stinson *et al.*, 1969). False positive decreases in QRS voltage may be produced by changes in impedance of the thorax, caused by pericardial fluid accumulation, pneumonia, pleural effusion, generalised oedema, and other factors. Normally, however, electrocardiographic voltage is remarkably constant, when the same machine and techniques are employed for all recordings. Measurement of serum levels of enzymes of myocardial origin is not helpful in the early diagnosis of graft rejection.

These diagnostic indices of cardiac rejection reflect already established graft damage. In recent years, therefore, efforts have been directed toward early detection of activation of the immune response by immunological monitoring and endomyocardial biopsy, in order to minimise rejection injury.

Immunological monitoring

Measurement of circulating levels of T lymphocytes (thymus derived), the putative mediators of cell-mediated immune injury, by spontaneous sheep erythrocyte rosette formation has proved to be a sensitive and useful assay for prediction of impending graft rejection (Bieber *et al.*, 1977). Since the assay can be performed daily, it provides a nearly continuous measure of the host immune status. Early postoperative administration of RATG, prednisone, and azathioprine causes profound depression of circulating T lymphocyte levels. T lymphocyte fractions less than 10 per cent (normally 65% of total circulating lymphocytes) are rarely associated with evidence of graft rejection, and therefore administration of RATG after the routine initial postoperative course is adjusted to maintain measured T lymphocyte fractions below this threshold during the first six postoperative weeks. Rises in T lymphocyte fractions above 10 per cent almost invariably herald overt graft rejection and usually occur one to three days before detectable histological changes. A major limitation of the T cell assay, however, is that after about six weeks there is no longer a close correlation between circulating T cell levels and graft rejection. Circulating T lymphocyte fractions gradually rise towards normal without subsequent graft rejection, therefore nullifying the predictive value of this assay in the later postoperative period.

Total serum rabbit globulin levels in patients treated with RATG can be serially measured by radioimmune assay (Bieber *et al.*, 1975). The data thus obtained allow characterisation of the disposition kinetics of RATG in individual patients.

During courses of RATG, serum rabbit globulin levels are inversely proportional to T lymphocyte counts; thus, low serum levels of rabbit globulin, resulting from either insufficient dosage or rapid clearance or both, are associated with an increased frequency and severity of rejection episodes and a decrease in late survival rates (Bieber *et al.*, 1977). Serial measurements of serum rabbit globulin levels are therefore used to determine both dosage and frequency of administration of RATG. Clearance rates do not remain static in individual patients, but usually decrease with repeated RATG courses (Bieber *et al.*, 1976).

Endomyocardial biopsy

The technique of percutaneous, transvenous endomyocardial biopsy of orthotopic cardiac grafts was developed in the laboratory in 1971 and applied clinically the following year (Caves *et al.*, 1973). Biopsy is performed by cannulation of the right internal jugular vein with a catheterisation sheath and passage of the biopsy forceps into the right ventricle under fluoroscopic control. Biopsies are usually performed weekly for the first six postoperative weeks, and also when impending rejection is suggested by changes in T lymphocyte levels, serum rabbit globulin levels, or electrocardiographic voltage. Because of its safety endomyocardial biopsy can be performed as frequently as indicated; early histologcal evidence of rejection can therefore be detected before development of graft dysfunction and treatment initiated before irreversible graft damage has occurred. Repeated biopsy also allows objective assessment of the response to antirejection therapy.

Treatment of acute rejection

A rise in the circulating T lymphocyte fraction during the early postoperative period is treated with increased RATG alone if biopsy fails to show histological evidence of acute rejection. If the results of biopsy are positive, however, the oral prednisone dose is increased to 1·5 mg/kg daily (with tapering to baseline levels during the ensuing two weeks) and 1 g methylprednisolone is given intravenously daily for three days. In the presence of adequate white blood cell and platelet counts actinomycin-D is given for two days in doses of 200 μg daily and heparin is administered intravenously for three to five days. Resolution of 95 per cent of rejection episodes can be expected with this treatment regimen.

Refractory prolonged acute rejection episodes are managed with additional methylprednisolone, RATG, and further treatment with actinomycin-D if tolerated. Refractory rejection is encountered most often in patients with rapid clearance of rabbit globulin, and for this reason antihuman thymocyte globulin of goat origin has recently been used in such patients. In several cases administration of rabbit and goat ATG on alternate days has resulted in reversal of apparently intractable rejection.

Chronic rejection

After the first three postoperative months the risk of acute graft rejection decreases conspicuously. Later, however, another form of graft injury may appear in the form of obliterative lesions of the donor coronary arteries. The onset of this process is insidious and its pathogenesis is probably related to antibody-mediated injury. Lesions of the coronary intima are at first entirely proliferative, but with time develop atherosclerotic characteristics. In order to assess the presence and rate of progression of such lesions coronary arteriography is performed yearly. At present, the incidence of graft arteriosclerosis, including minor disease, is approximately 35 per cent at five years. This incidence is much less than that observed in patients undergoing transplantation before 1970, when indefinite prophylaxis with an antithrombotic regimen consisting of dipyridamole and warfarin was initiated (Griepp *et al.*, 1977b). Because of its continuing occurrence, serial study is necessary, and six patients have undergone cardiac retransplantation because of critical graft arteriosclerosis. As a result of recent analysis, warfarin has not been used as an item of regular treatment since January 1979, but antiplatelet therapy with dipyridamole has been retained; other regimens of potential benefit are at present being assessed in the laboratory.

Complications of treatment

INFECTION

The majority of deaths after cardiac transplantation in the Stanford series have been the result of infection. One hundred and forty-seven patients suffered from at least one episode of infection. Pulmonary infections are the most common, and cardiac transplant recipients appear to be more prone to such infections than other transplant patients because of preoperative pulmonary congestion, thoracotomy, cardiopulmonary bypass, and endotracheal intubation. Other types of infection encountered in these patients are summarised in Table 1; blood stream, central nervous system, and urinary tract infections are also common. Because of the high incidence of infections and the broad range of both ordinary and opportunist pathogens,

Table 1 *Infections in Stanford cardiac transplantation patients*

	No. of episodes	*No. of patients*
Pulmonary infection	217	108
Empyema	10	10
Septicaemia	46	38
Urinary tract infection	31	22
Disseminated fungal	6	6
Disseminated viral	8	8
Central nervous system	15	15
Hepatitis	6	5
Miscellaneous	107	78
Retinitis	4	4
Osteomyelitis	1	1

Table 2 *Stanford cardiac transplantation—infecting organisms*

	No. of infections	*No. of patients*	*No. associated with fatal outcome*
Fungal			
Aspergillus fumigatus	38	38	18
Candida	9	9	4
Coccidioides	1	1	
Cryptococcus	7	7	1
Mucor	1	1	1
Rhizopus	2	2	
Yeast, unidentified	1	1	1
Nocardia	21	21	3
Bacterial			
Anaerobic mixed	34	28	5
Arizona hinshawii	2	2	1
Atypical acid-fast bacilli	9	8	
Citrobacter	4	4	
Clostridium sp	2	2	
Enterobacter	12	10	6
Escherichia coli	44	37	16
Haemophilus parainfluenzae	13	8	1
Herellea vaginicola	3	3	
Klebsiella	42	40	20
Listeria	4	4	
Mima polymorpha	1	1	
Proteus mirabilis	5	3	1
Proteus morganii	1	1	
Pseudomonas sp	24	19	8
Salmonella typhimurium	1	1	
Serratia	16	15	5
Staphylococcus aureus	26	22	5
Streptococcus pneumoniae	5	5	1
Other Streptococcus sp including enterococci	23	20	6
Viral			
Cytomegalovirus	9	9	2
Hepatitis	4	4	1
Herpes simplex	38	37	1
Herpes zoster	23	23	2
Influenza A	3	2	
Unidentified	3	3	1
Protozoan			
Pneumocystis	16	15	4
Toxoplasma	5	5	4
Trichomonas	1	1	1

diagnostic procedures must be aggressive and complete. For example, when pulmonary infection is suspected bronchial aspiration is performed as an initial diagnostic procedure. Transthoracic needle aspiration of the lung is often performed when radiological findings suggest fungal or protozoan infection or when there is any pulmonary infection of obscure aetiology.

The list of infecting agents encountered in our series (Table 2) illustrates the prominence of opportunist pathogens. Despite the severity of such infections in patients who have had large doses of immunosuppressive agents, however, rapid diagnosis and aggressive treatment have resulted in successful resolution in most cases.

MALIGNANT DISEASE

The incidence of *de novo* malignant disease after cardiac transplantation is similar in our series to that described for renal transplantation (overall 6%). Thirteen malignant lesions have been diagnosed in the total 161 recipients. These included five carcinomas (four skin, one colon), two cases of acute myeloid leukaemia, and six lymphomas. All the lymphoproliferative diseases occurred in patients whose original diagnosis was idiopathic cardiomyopathy; such patients constitute only 41 per cent of our transplant population (Krikorian *et al.*, 1978). Moreover, all have been in the younger age range (15 to 30 years). Four patients have died of malignant disease, and the remainder, including four with *de novo* lymphomas, have survived with appropriate treatment.

Outpatient care

The average hospital stay after transplantation is 55 days. After discharge patients are initially seen twice weekly in the outpatient clinic, and thereafter the frequency of outpatient examination is progressively decreased, in the absence of complications, to once monthly. Patients who remain clinically stable return after two or three months to the care of their referring physicians.

Infection and graft rejection are the principal hazards for long-term cardiac recipients. At each outpatient visit, therefore, evidence of such potential complications is sought. Physical findings suggestive of graft rejection include arrhythmias, a diastolic gallop rhythm, a pericardial friction rub, and congestive heart failure. Such findings, either alone or in association with electrocardiographic changes, may require repeat transvenous endomyocardial biopsy on either an outpatient or inpatient basis. Chest *x*-ray films and electrocardiograms are obtained, and routine biochemical tests include measurement of serum lipids. Hyperlipidaemia, if persistent, is treated with appropriate agents.

Maintenance treatment, other than that required for indefinite immunosuppression, often includes diuretics and supplementary potassium because of the salt-retaining effect of prednisone. The initial treatment of acute rejection episodes diagnosed in the outpatient department on clinical and electrocardiographic criteria (with or without endomyocardial biopsy) generally consists of temporary increase of prednisone dosage to 50 mg twice daily, followed by a daily reduction of the dose by 5 mg to a level 10 mg above prerejection maintenance dosage. Further tapering is accomplished slowly. If complete reversal of signs of acute rejection does not occur within several days, the recipient is admitted for endomyocardial biopsy, and intravenous methylprednisolone and RATG are given as described for early postoperative acute rejection episodes. The maintenance dose of azathioprine is continued according to bone marrow tolerance.

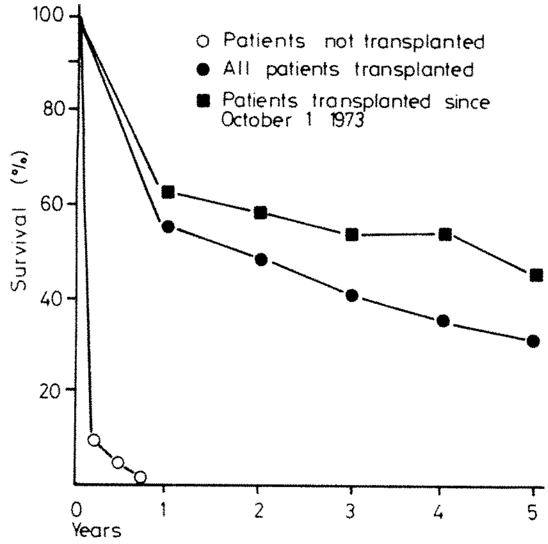

Fig. *Survival rates calculated by actuarial method for patients undergoing transplantation and for those selected for transplantation but who died before a donor could be found.*

Survival rates

Survival rates, calculated by the actuarial method, for patients undergoing transplantation and for recipients selected for transplantation but who died before a suitable donor became available are shown in the Figure.

Survival rates have improved significantly since 1973, coincident with the introduction of the endomyocardial biopsy technique in routine clinical management, the use of ATG of rabbit origin, and the refinement of immunological monitoring methods. In 94 consecutive patients undergoing transplantation since 1973, the survival rates at one, two, three, and four years were 63 per cent (±5·2SE), 58 per cent (±5·4), 54 per cent (±5·8), and 54 per cent (±5·8), respectively. These figures compare favourably with graft survival rates in recipients of cadaveric renal transplants; in most large series the one-year graft survival rate is approximately 50 per cent (Renal Transplant Registry, 1977); 90 per cent of surviving cardiac recipients in the Stanford programme have returned to full activity and the majority have resumed active employment.

Discussion

The experience described in this report has shown that cardiac transplantation can be effective treatment for selected patients with end-stage cardiac failure not amenable to treatment by any other means. Current survival figures are equal or superior to graft survival rates for renal transplants from unrelated donors. These results may encourage those in other centres to renew their interest in clinical cardiac transplantation.

It is not absolutely necessary for clinical heart transplantation to be performed in a centre with established renal and/or hepatic transplant programmes (cardiac transplantation is the only form of organ transplantation at present performed at Stanford). The diagnosis and management of cardiac allograft rejection differs from that of rejection in the case of other organ transplants, and it should be emphasised that a fully trained and committed staff accustomed to early and long-term postoperative care of cardiac surgical patients is essential for a successful effort in cardiac transplantation.

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Effect of isocapnic hypoxia on systolic time intervals in conscious man

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SUMMARY The effects of progressive isocapnic hypoxia on the systolic time intervals were studied in 10 healthy human subjects. We induced hypoxia by a rebreathing method and monitored the arterial oxygen saturation continuously and non-invasively by means of an ear oximeter. Arterial oxygen saturation (S_aO_2) was allowed to fall to a level of 75 per cent and was then held constant for five minutes. As S_aO_2 fell, heart rate increased linearly, with a mean increase of 0·83 beats/min per one per cent fall in S_aO_2. The pre-ejection phase index decreased from a mean of 127·2 ms at full oxygen saturation to 120·1 ms at steady-state hypoxia levels, while the ratio of the pre-ejection phase to left ventricular ejection time decreased from a mean of 0·330 to 0·301. The left ventricular ejection time index increased from 417·4 ms to 429·3 ms, while no statistically significant difference was found in the length of electromechanical systole.

The use of systolic time intervals (STI) is a well-established method for assessing cardiovascular function non-invasively (Weissler and Garrard, 1971a, b; Lewis *et al.*, 1977; Weissler, 1977). As hypoxia is common in clinical practice, its effect on systolic time intervals (STI) has received considerable attention, but the reported findings are conflicting, as the duration of hypoxia was variable, and in most studies the P_{CO_2} was allowed to vary, making it difficult to assess the effect of hypoxia alone. We recently reported the effect of acute, progressive hypoxia on heart rate in healthy subjects using a technique that enabled us to study physiological responses independent of changes in P_{CO_2} (Slutsky and Rebuck, 1978). We found that heart rate was best fitted to an inverse linear relation to arterial oxygen saturation and a power function to P_{O_2}. The purpose of the present study was to extend these findings, determining whether the tachycardia induced by isocapnic hypoxia was associated with changes in electromechanical systole.

Subjects

Ten subjects (5 men, 5 women), aged 24 to 40, who were staff members of Toronto General Hospital (laboratory personnel, nurses, and physicians) were studied. All subjects were physically fit, had normal ventilatory function, and no historical or physical evidence of cardiovascular disease. Subjects had not taken any drugs for the 24 hours before the experiment, and were asked not to smoke and not to drink coffee or tea within two hours of study. All studies were performed in the morning. Informed written consent was given by all subjects.

Methods

INDUCTION OF HYPOXIA

The principle of the technique was to have the subject rebreathe from a 6-litre bag which initially contained room air. Oxygen was added to the bag at a rate of 100 ml/min, that is less than the subject's oxygen consumption, so that the P_{O_2} fell progressively but slowly during rebreathing. End-tidal P_{CO_2} was held constant at a predetermined level by means of a variable-speed pump attached to a soda-lime CO_2-absorbing bypass. Arterial oxygen saturation was measured continuously with a fibreoptic ear oximeter (HP 47201A) (Saunders *et al.*, 1976). Details of the experimental circuit have been described previously (Rebuck and Woodley, 1975).

When the subject had been lying comfortably for 15 minutes, he/she began breathing room air

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through the mouthpiece while end-tidal P_{CO_2} was monitored. After a stable end-tidal P_{CO_2} had been achieved (±1 mmHg), the valve connecting the subject to the rebreathing circuit was turned at the end of a normal expiration to allow rebreathing and hence progressive lowering of the inspired P_{O_2}. When the subject's oxygen saturation reached a value of 70 to 75 per cent, he/she was maintained at that level for five minutes. Thereafter, the subject was disconnected from the circuit by turning the valve connecting the subject to the rebreathing bag. However, the subject continued to breathe room air via the mouthpiece until his/her oxygen saturation was equal to or greater than his/her prehypoxic level for at least five minutes.

Tidal gas was sampled at the mouth, passed through a Beckman LB-2 rapid CO_2 analyser (Beckman Instruments, I 11) and a Servomex oxygen analyser (Type OA 272), before being returned to the rebreathing bag. Inspired ventilation was measured with a Med. Sci. 570 wedge spirometer (St. Louis, Mo.). Ventilation, P_{O_2}, P_{CO_2}, and S_aO_2 were recorded on an eight-channel graphic recorder (Astromed. Super 8).

SYSTOLIC TIME INTERVALS

Simultaneous recording of the electrocardiogram, phonocardiogram, indirect carotid artery pulse tracing, and arterial oxygen saturation were recorded using an Elema-Schonander eight-channel recorder at a paper speed of 100 mm/s. The carotid pulse was obtained by holding a pressure cup over the right carotid artery. The pressure cup was connected through polyethylene tubing in series with an air-coupled transducer whose frequency response was 0·1 to 40 Hz. An Elema-Schonander piezo-microphone with a low band pass filter was used to record the heart sounds; the frequency response of the phonocardiograph was 100 to 400 Hz. A standard electrocardiogram (lead II) was used to identify the Q wave. All subjects were studied in the resting supine position, and carotid pulse tracings were taken at full oxygen saturation and at approximately 4 per cent decrements as arterial oxygen saturation decreased. Tracings were also obtained at one-minute intervals during the five minutes of steady-state hypoxia at a saturation of approximately 75 per cent.

Analysis of data

The arterial oxygen saturation and the duration of the components of the STI were calculated from these tracings using a digitiser (Model no. HP-9864A) connected to a calculator (Model no. 9820A). The digitiser had an accuracy of 0·01 inch in the X and Y co-ordinates. This system has been considered by others to be the most accurate means of calculating STI (Lewis *et al.*, 1977). Heart rate was calculated from the Q-Q interval of the electrocardiogram. Electromechanical systole (QS2) was measured from the initial QRS deflection of the electrocardiogram to the initial high-frequency vibrations of the aortic component of the second heart sound. Left ventricular ejection time (LVET) was measured from the onset of the rapid upstroke to the trough of the incisura. Pre-ejection phase (PEP) was obtained by subtracting the LVET from the QS2. The STI were then corrected for heart rate according to sex of the subject, using the previously-described equations (Weissler *et al.*, 1968) to obtain the STI indices: QS2I, LVETI, and PEPI.

Linear regression was used to determine the effect of saturation on each of the dependent variables. The paired t test was used to determine whether any statistical differences existed in the dependent variables at full saturation and during hypoxia.

Results

Heart rate increased linearly in all subjects as arterial oxygen saturation fell, with a mean heart rate increase of 0·83 beats/min per 1 per cent fall in saturation and mean correlation coefficient of 0·92 (Table).

The ratio, PEP/LVET, decreased in all subjects as progressive hypoxia was induced (Fig.). The mean value of PEP/LVET was 0·330 at full saturation, well within the accepted range (0·350 ±0·04) for healthy subjects (Weissler and Garrard, 1971a). The value of PEP/LVET at the steady-state hypoxia level ($S_aO_2 \sim 75\%$) was 0·301, a value which was statistically different, using a paired t test, from the value at full saturation ($P < 0·01$) (Table).

LVETI increased in all but one subject with a mean value of 417·4 ±10·39 ms to 429·3 ±9·14 ms as saturation was decreased to steady-state hypoxia levels ($P < 0·01$) (Fig.). This increase in LVETI during arterial desaturation was well described by linear equations in all but two subjects. The average correlation coefficient for all subjects was 0·77. The decrease in PEPI from a mean value of 127·2 ± 7·15 ms to 120·0 ±8·80 ms was also statistically significant ($P < 0·05$) (Fig.).

The changes in PEPI and LVETI, which were in opposite directions, were such that the mean value of QS2I (=PEPI+LVETI) at full saturation (544·6 ±13·07 ms) and at the steady-state hypoxia levels (549·6 ±12·21 ms) were almost the same (Fig.). These changes in QS2I were not statistically significant (Table).

Table *Mean heart rates (±SD) and STI (±SD) at full arterial oxygen saturation ($S_{a}o_{2}\sim 97\%$), at a steady-state hypoxia ($S_{a}o_{2}\sim 75\%$)*

	Full saturation (97%)	*Steady-state hypoxia (75%)*	*t value*	*Statistical significance (P)*
Heart rate (beats/min)	71·4 (±8·13)	91·8	12·23	P<0·001
PEP/LVET	0·330 ±0·020	0·301 ±0·029	4·03	P<0·01
PEPI (ms)	127·2 ±7·15	120·1 ±8·80	2·96	P<0·05
LVETI (ms)	417·4 ±10·39	429·3 ±9·14	4·42	P<0·01
QS2I (ms)	544·6 ±13·07	549·6 ±12·21	1·76	NS

Note: There is a significant increase in heart rate and LVETI, a significant decrease in PEP/LVET and PEPI, with no significant difference in QS2I.

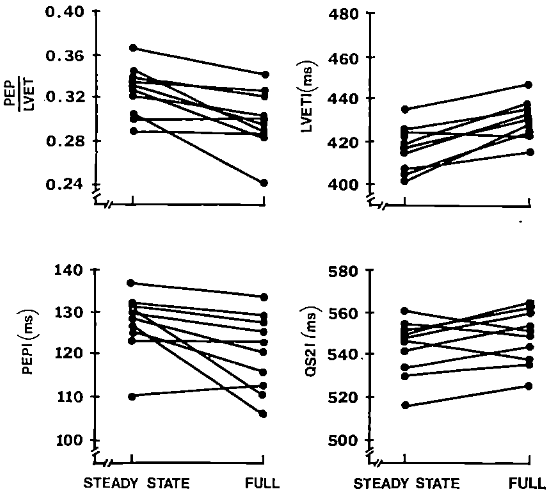

Fig. *Values of PEP/LVET, LVETI, PEPI, and QS2I at full arterial oxygen saturation ($S_{a}o_{2}\sim 97\%$) and at steady-state hypoxia ($S_{a}o_{2}\sim 75\%$). All subjects showed a decrease in PEP/LVET and an increase in LVETI when arterial oxygen saturation was reduced to 75 per cent. In nine of 10 subjects PEPI decreased and in seven of 10 subjects QS2I decreased during hypoxia. The changes in PEP/LVET, LVETI, and PEPI were statistically significant.*

Discussion

Analysis of the systolic time intervals (STI) provides a non-invasive method for investigating the cardiovascular system. The indices determined using these methods are primarily measures of left ventricular performance (Weissler *et al.*, 1969; Lewis *et al.*, 1976). Though STI have limited use in differential diagnosis, they serve to quantify the effects on the cardiovascular system of various pharmacological interventions (Harris *et al.*, 1966, 1967) or disease states (Weissler *et al.*, 1968; Toutouzas *et al.*, 1969; Lewis *et al.*, 1976), as multiple observations in the same individual are possible.

Some studies have reported the effects of hypoxia on the STI in conscious man, but in these studies the Pco_2 was allowed to vary as a consequence of alveolar ventilation. Thus the effects of hypoxia alone on the STI could not readily be assessed. As hypocapnia and alkalosis have important effects on the circulatory system (Richardson *et al.*, 1972), it is likely that they may also influence the STI independently of the effect of hypoxia. The purpose of the present study was to isolate the effects of hypoxia on the STI by inducing progressive isocapnic hypoxia in conscious humans using a technique developed by us that combines rebreathing, oximetry, and precise control of Pco_2 (Rebuck and Woodley, 1975). The linear increase in heart rate that we found with decreasing levels of arterial oxygen saturation is in agreement with our previous study in which we found that isocapnic hypoxia induced a mean increase in heart rate of 0·98 beats/min per 1 per cent fall in saturation (Slutsky and Rebuck, 1978). This tachycardia was accompanied by a decrease in PEP/LVET and PEPI, an increase in LVETI, while QS2I remained the same.

It emerges that our findings concerning the STI are in agreement with those of Kowalsky and Anthony (1972), who induced hypoxia in their subjects by taking them to simulated altitudes of 15 000 and 18 000 ft at a rate of 3000 ft/min in a hypobaric chamber. Values for Pco_2 were not given in their study, but no attempt was made to monitor or control alveolar ventilation. On the other hand, these results contrast with those of Balasubramanian *et al.* (1975) who studied the effects of high-altitude hypoxia on the STI by exposing healthy sea-level residents to high altitude over several days. They found an increase in PEP/LVET and PEPI with a decrease in LVETI. In their study, the first measurements of the STI were performed one day after the subjects had been at the high altitude so that the process of acclimatisation may have started to develop. Furthermore, the greatest changes in the STI occurred on the second and third days at high altitude and, though changes decreased by the tenth day, the mean PEP/LVET were significantly lower than the baseline readings. As these changes are found characteristically in patients with left ventricular failure, it was proposed that they might relate to the pathophysiology of high-altitude pulmonary oedema.

The only studies on the effects of isocapnic hypoxia on the STI that we are aware of are those of Rasmussen and Bech-Jansen (1974) and Rasmussen *et al.* (1975) in anaesthetised, artificially ventilated dogs. They found that there was a slight decrease in PEP/LVET and a slight increase in $1/\text{PEP}^2$ when the arterial partial pressure of oxygen (P_aO_2) fell from 120 to 80 mmHg and that these changes were not obvious until the P_aO_2 had fallen below 40 mmHg. After approximately 25 minutes of severe hypoxia ($P_aO_2 = 20$ mmHg), PEP/LVET started to increase towards their initial values as $1/\text{PEP}^2$ started to decrease. This observation in anaesthetised dogs may explain, in part, the similarity in results observed by us and by Kowalsky and Anthony (1972), as both studies used relatively short periods of hypoxia, as opposed to Balasubramanian *et al.* (1975) in whose subjects the stimulus persisted for days rather than minutes. However, caution is required in extrapolating the results from severe hypoxia in anaesthetised ventilated animals to conscious man, as in rabbits (Korner, 1959; Korner and Edwards, 1960) and in artificially ventilated dogs (Bernthal *et al.*, 1951) hypoxia induced bradycardia rather than an increase in heart rate.

Hypoxia induces a number of physiological changes which may, in part, explain our findings. The mechanism by which hypoxia causes an increase in heart rate is thought to be an integration of carotid body reflexes and reflexes secondary to the hyperpnoea induced by hypoxia (Daly, 1972). When the carotid body is perfused with hypoxic blood, a decrease in myocardial contractility occurs (Downing *et al.*, 1962, 1963), while isolated cerebral hypoxia or total body hypoxia causes an increase in myocardial contractility. This is in keeping with our findings of a decrease in PEP/LVET, a ratio which is considered to reflect left ventricular performance (Lewis *et al.*, 1977) and which correlates well with angiographic ejection fraction (Garrard *et al.*, 1970).

Our studies may allow some speculation as to the relative roles of adrenergic and mechanical factors in the tachycardia of hypoxia. Acute hypoxia stimulates the adrenal medulla either directly or via the sympathetic nervous system (Van Liere and Stickney, 1963), and beta-receptor stimulation has been shown to cause a decrease in PEP/LVET (Weissler, 1977) and a decrease in PEPI. However, positive inotropic agents generally shorten the LVETI and QS2I (Harris *et al.*, 1967; Salzman *et al.*, 1971; Lewis *et al.*, 1972), while we found that LVETI increased and QS2I remained approximately the same. Since QS2I is felt to be the most useful of the STI in judging the presence of positive inotropic stimulation (Lewis *et al.*, 1977), it is unlikely that the effects we have observed are solely the result of catecholamine release though this may play some role. This finding is in agreement with those of Richardson *et al.* (1967) who found no increases in plasma concentrations of adrenaline or noradrenaline during hypoxia. Decreased vagal tone does not seem to be the mechanism causing the changes we observed as it causes both QS2I and LVETI to shorten while PEPI remains the same (Raab *et al.*, 1958).

The levels of hypoxia we have used have little effect on blood pressure, but more profound hypoxia can cause a decrease in peripheral resistance (Van Liere and Stickney, 1963). Though Shaver *et al.* (1968) showed that an increase in afterload causes an increase in PEPI, LVETI, and QS2I, in the two subjects they studied in greater detail, they also found that left ventricular end-diastolic pressure had also increased significantly. The STI are sensitive both to changes in preload (Sawayama *et al.*, 1969; Shah *et al.*, 1969) and to alterations in posture. A change from lying to standing induces significant increases in PEPI and PEP/LVET. Shah *et al.* (1969) showed that decreasing preload in normal subjects by the application of venous cuffs on both thighs was associated with an increase in PEPI and PEP/LVET, while systemic artery systolic and diastolic pressures did not change significantly. Though in dogs hypoxia causes an increase in pulmonary wedge pressure, an increase in left atrial pressure does not occur, perhaps because there is constriction between the site of arterial wedging and the left atrium (Braunwald *et al.*, 1958).

Acute hypoxia has been shown to cause a decrease in total peripheral resistance and an increase in stroke volume (Van Liere and Stickney, 1963). The latter causes an increase in LVETI, a decrease in PEPI, while leaving QS2I unaltered (Weissler *et al.*, 1961; Willems and Kesteloot, 1967; Greenfield *et al.*, 1968). As these are precisely the findings we obtained in our study, it is likely that our results may be explained by a combination of changes in peripheral resistance and stroke volume. We conclude that in conscious man, heart rate increases linearly, with falls in arterial oxygen saturation, and that the tachycardia is not associated with a shortening of electromechanical systole, corrected for heart rate. Since catecholamines are known to shorten QS2I, this finding that QS2I remained constant suggests that increased adrenergic activity is not responsible for the tachycardia induced by isocapnic hypoxia. It is more likely that the tachycardia is associated with an increased stroke volume, possibly combined with an increase in preload. However, these findings may be much influenced by the duration of exposure to hypoxia and may be obscured if the hypoxia is combined with respiratory alkalosis.

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Retrograde catheterisation of left atrium

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SUMMARY Retrograde catheterisation of the left atrium using a no. 8 F pigtail catheter introduced percutaneously via a femoral artery was successfully accomplished in 48 out of 50 patients undergoing diagnostic cardiac catheterisation. There was one episode of ventricular fibrillation requiring cardioversion (without sequelae), and one episode of ventricular tachycardia which was self-terminating, but no other complications and no deaths. The average fluoroscopy time was four minutes.

There are two methods for recording the left atrial pressure: indirect and direct.

The indirect technique relies on measurement of the pulmonary artery wedge pressure. This method is simple and reliable and can be performed at the bedside using balloon-tipped catheters.

The direct method can be accomplished in one of three ways:

(a) Via a probe through a patent foramen ovale which is present in approximately 10 per cent of adult patients undergoing diagnostic studies (Iskandrian *et al.*, 1977).

(b) Transseptal puncture using specially designed needles and catheters (Ross *et al.*, 1959; Verel, 1967).

(c) Retrograde transaortic transmitral approach using Shirey's catheter (Shirey and Sones, 1966), when using the brachial artery approach for left heart catheterisation. Unfortunately, both transseptal puncture and the retrograde Shirey technique require considerable skill and are not entirely free of morbidity and even mortality (Ross *et al.*, 1959; Shirey and Sones, 1966).

We describe a new and simple technique for left atrial catheterisation that can be accomplished safely and rapidly in laboratories using the percutaneous femoral artery approach for left heart catheterisation with a standard percutaneous catheter.

Subjects and methods

This study was carried out on 50 adult patients selected at random who were undergoing diagnostic cardiac catheterisation. Each patient underwent left and right heart catheterisation in the fasting state via the right femoral artery and vein under local anaesthesia with lignocaine. Pressures were monitored and recorded on an Electronic for Medicine recorder.

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TECHNIQUES FOR LEFT ATRIAL CATHETERISATION

We routinely use a no. 8 French pigtail catheter (Cordis) for left heart catheterisation with the percutaneous femoral artery approach. The catheter tapers to a no. 6 French near the tip and is provided with a pigtail loop 1·2 cm in diameter, and end hole, and 12 side holes. The catheter is advanced from the left cusp of the aortic valve into the left ventricle and the patient is positioned in a shallow right anterior oblique projection. A superiorly directed loop is formed in the left ventricular cavity and the loop enlarged by further advancement of the catheter with counter-clockwise rotation. Once the pigtail enters the left atrium, the catheter is withdrawn with gentle clockwise rotation. The pressure is continuously monitored during the procedure. A number of trials may be necessary in some patients in order to find the right size of the loop. Fig. 1 illustrates the steps during manipulation of the catheter for left atrial catheterisation.

Results

There were 37 men and 13 women, with a mean age of 46 years. Thirty-five patients had coronary artery disease, five had cardiomyopathy, four had mitral valve regurgitation, one had mild mitral stenosis (mitral valve area of 1·8 cm^2), and five had no organic heart disease.

Fig. 2 shows cine frames of the position of the

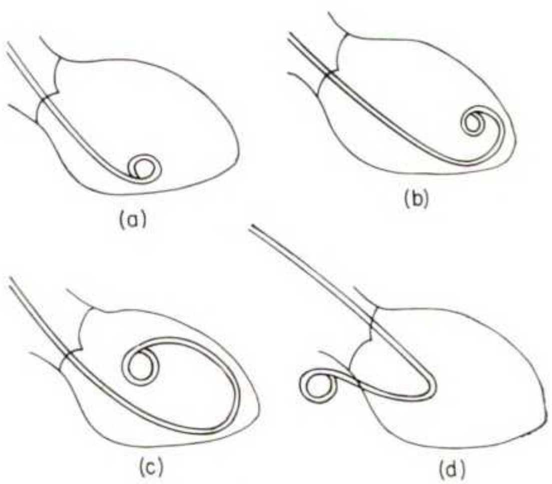
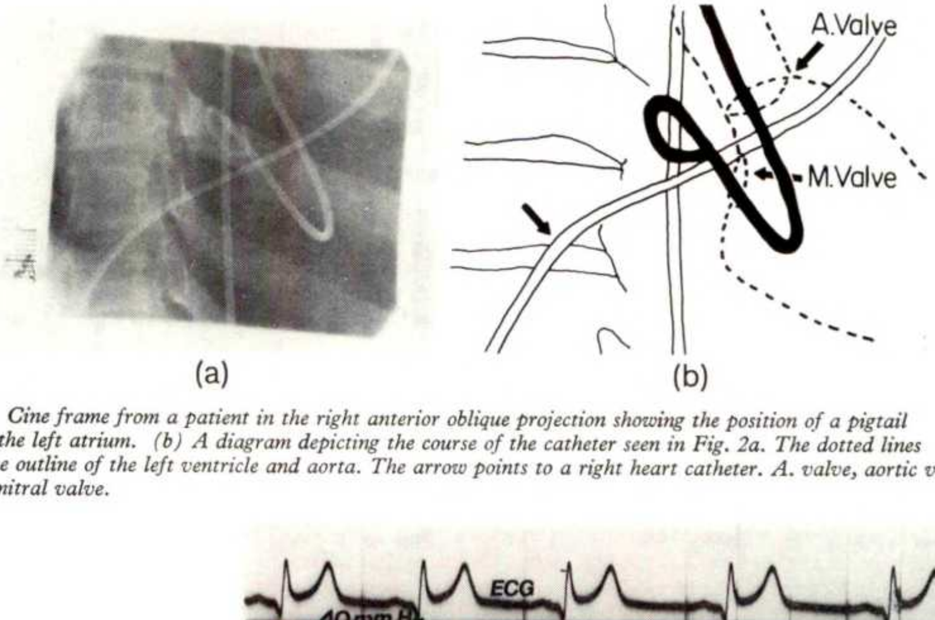


Fig. 1 *Diagram of retrograde left atrial catheterisation using a pigtail catheter.* (a) *The tip of the catheter is in the ventricular cavity;* (b) *a loop is formed in the left ventricle;* (c) *the loop is enlarged with counterclockwise rotation;* (d) *the loop is advanced into the left atrium and rotated clockwise.*



(a) (b)

Fig. 2*(a)* *Cine frame from a patient in the right anterior oblique projection showing the position of a pigtail catheter in the left atrium. (b) A diagram depicting the course of the catheter seen in Fig. 2a. The dotted lines represent the outline of the left ventricle and aorta. The arrow points to a right heart catheter. A. valve, aortic valve; M. valve, mitral valve.*

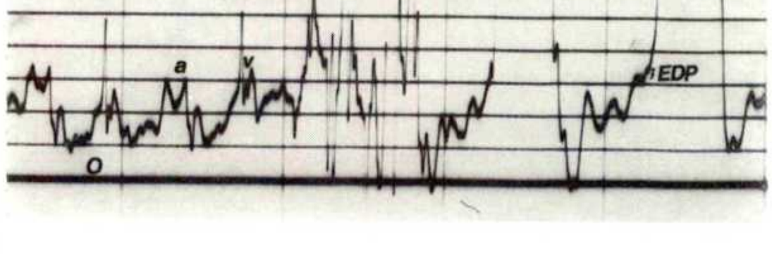


Fig. 3 *A pullback pressure tracing from the left atrium (LA) into the left ventricle (LV) on a scale of 0 to 40 mmHg. EDP indicates end-diastolic pressure; A and V are the left atrial pressure waves.*

pigtail catheter in the left atrium in the right anterior oblique projection.

Fig. 3 is a pullback pressure tracing from the left atrium into the left ventricle in a patient with normal pressures.

Fig. 4 is a pullback pressure tracing from a patient with mitral regurgitation showing large 'V' waves in the left atrium.

Fig. 5 is a tracing of simultaneous left atrial and pulmonary artery wedge pressures from the same patient as in Fig. 4, showing that the left atrial pressure tracing is free of catheter artefacts and would almost be superimposed on the wedge pressure tracing.

COMPLICATIONS

Retrograde left atrial catheterisation was successfully accomplished in 48 out of the 50 patients including all with valvular heart disease. Ventricular extrasystoles and short runs of ventricular tachycardia (three to four complexes in a row) are common during the procedure, but disappear promptly upon withdrawal of the catheter. One patient developed ventricular fibrillation which required DC countershock; this did not necessitate premature termination of the catheterisation. One patient developed prolonged ventricular tachycardia that stopped when the catheter was withdrawn. There were no deaths and no other complications. In two patients, the procedure failed, because of extreme ventricular irritability in one patient, and for no obvious reason in the other. The average fluoroscopy time was four minutes (range 2 to 10 minutes). The pressure tracings were all of excellent quality. Though we did not see it in our study, there is a possibility of dislodging emboli from clots in the left ventricle or left atrium.

Discussion

Retrograde left atrial catheterisation using a pigtail catheter is a safe, rapid, and reliable technique for

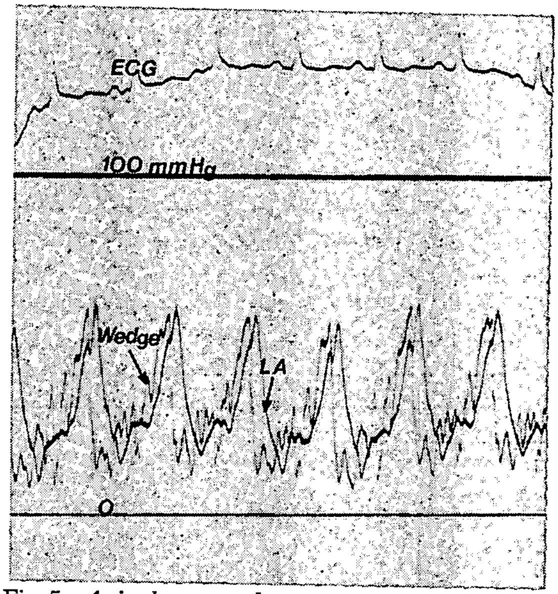


Fig. 5 *A simultaneous pulmonary artery wedge and left atrial (LA) pressure tracing from the same patient as in Fig. 4 showing both pressures can be superimposed.*

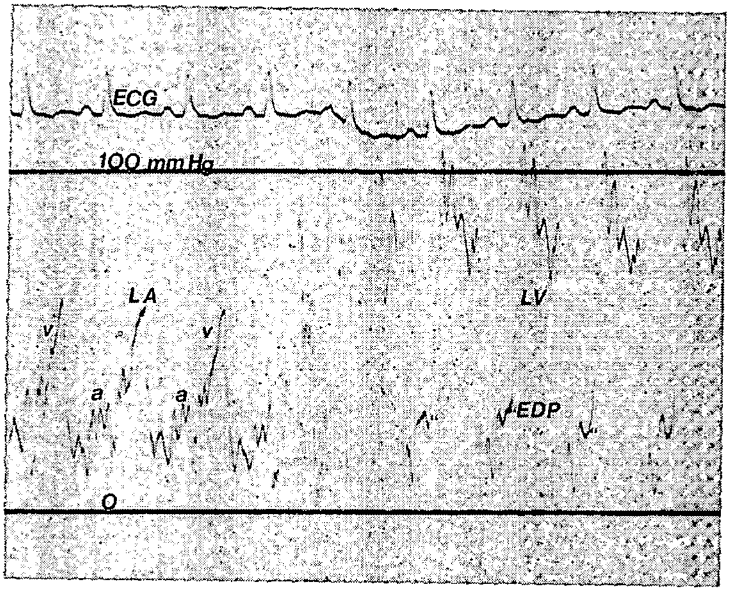


Fig. 4 *A pullback pressure tracing from the left atrium into the left ventricle on a scale of 0 to 100 mmHg from a patient with mitral regurgitation showing large 'V' waves.*

measuring the left atrial pressure. The indications for direct left atrial pressure recording are limited since pulmonary artery wedge pressure reliably reflects the left atrial pressure and can be performed safely and rapidly. However, at times wedge pressure recording may be very difficult if not impossible, especially in patients with mitral valve disease associated with significant pulmonary hypertension and dilatation of the pulmonary artery, right ventricle, and right atrium. Wong *et al.* (1975) suggested that retrograde left atrial catheterisation may be useful in patients with hypertrophic cardiomyopathy. A pullback from the left atrium into the inflow tract of the left ventricle ensures proper position of the catheter and excludes cavity obliteration or catheter entrapment. Other indications may include: (1) possible pulmonary venous obstruction; (2) when it is necessary to know left atrial or pulmonary venous saturation, to calculate the size of coexisting intracardiac and intrapulmonary shunts; (3) inability to enter the pulmonary artery; then a pulmonary vein wedge pressure may be used as a reflection of pulmonary artery pressure (such as in patients with truncus arteriosus). The pigtail catheter can be exchanged for an end hole or a double lumen catheter over an exchange wire; (4) suspicion of a small left-to-right shunt not proven by oximetry or dye dilution techniques, particularly when this coexists with another large shunt: here, a left atrial angiogram may be useful; (5) when right heart catheterisation is not performed (that is patients having left heart catheterisation and angiography only), but where measurement of the left atrial pressure is likely to yield important information, for example patients with high left ventricular end-diastolic pressure primarily caused by a prominent atrial 'kick'; in such patients the mean left atrial pressure could be substantially lower than the left ventricular end-diastolic pressure, and thus may not only explain why signs and symptoms of pulmonary congestion are absent in spite of the presence of very high left ventricular end-diastolic pressure, but also help to define the appropriate level of hydration and/or medications; (6) when transseptal puncture cannot be used because of severe right atrial enlargement, kyphoscoliosis, thrombophlebitis of the lower extremities, inferior vena caval ligation, or altered anatomical relations of the great vessels. This technique can also be used in laboratories performing catheterisations via the brachial artery. While the indications listed above are uncommon, we have encountered all in the past three years. The need to catheterise the left atrium is not always evident before the procedure; familiarity with this technique and its use has enabled us to obtain a complete diagnostic study. Arrhythmias have been of no more consequence to the patient than those encountered during other catheter manipulations (that is left ventriculography). The technique may be used whenever the direct left atrial pressure or left atrial oxygen saturations or left atrial angiography are essential for diagnostic evaluation.

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Role of right ventricular infarction in cardiogenic shock associated with inferior myocardial infarction[1]

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SUMMARY In order to assess the role of right ventricular and left ventricular dysfunction in patients with cardiogenic shock associated with combined right ventricular and inferior myocardial infarction, we reviewed the clinical records and haemodynamic data of 18 patients with inferior myocardial infarction and cardiogenic shock. Six of these patients had haemodynamic evidence of right ventricular dysfunction. There was no significant difference in left ventricular stroke work index between patients with (18±3 g m per m^2) and without (14±2) associated right ventricular dysfunction. Though pulmonary artery wedge mean pressure was significantly lower in patients with right ventricular dysfunction (10±1 mmHg) than in those without right ventricular dysfunction (18±2), this difference is probably the consequence of the right ventricular damage, since all patients with right ventricular dysfunction had a wedge pressure 11 mmHg or less compared with only three of 12 patients without right ventricular impairment. Necropsy observations in eight patients including two with right ventricular dysfunction support this concept. All patients had 40 per cent or more infarction (old plus new) of the left ventricle. However, the two with right ventricular infarction had wedge pressures 10 mmHg or less whereas the other six without right ventricular infarction all had wedge pressure 14 mmHg or more. In addition, while all five patients with right ventricular dysfunction who were treated by plasma volume expansion had a rise in wedge pressure (16±1 after fluid therapy) only two survived. Mortality in the group with right ventricular dysfunction (three of six) was similar to that in the group without right ventricular dysfunction (seven of 12). We conclude that in patients with cardiogenic shock associated with combined right ventricular and inferior myocardial infarction, (1) low pulmonary artery wedge pressure is the result primarily of right ventricular dysfunction and does not necessarily imply that left ventricular damage is slight and (2) severe left ventricular damage, often with a relatively low wedge pressure, is more common than has been previously reported in these patients.

Recently, a number of investigators (Rigo *et al.*, 1975; Sharpe *et al.*, 1978; Tobinick *et al.*, 1978) have drawn attention to the frequency with which inferior myocardial infarction is complicated by right ventricular infarction. The typical haemodynamic feature of this entity is a raised mean right atrial pressure which equals or exceeds mean pulmonary artery wedge pressure (Cohn *et al.*, 1974; Rotman *et al.*, 1974). Furthermore, some authors (Cohn *et al.*, 1974; Rigo *et al.*, 1975) have reported data from a few patients suggesting that when shock occurs in inferior myocardial infarction associated with right ventricular infarction, this is primarily related to right ventricular dysfunction, with only modest impairment of left ventricular function. However, in both early (Rigo *et al.*, 1975) and more recent (Sharpe *et al.*, 1978) reports, other patients with haemodynamic and morphological evidence of severe right ventricular dysfunction in association with inferior myocardial infarction have had a normal cardiac output and systemic arterial pressure. This suggests that it is the status of the left ventricle which determines whether shock develops in patients with combined inferior and right ventricular myocardial infarction. The present study was undertaken in order to examine the role

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of right ventricular and left ventricular dysfunction in the pathogenesis of cardiogenic shock associated with combined right ventricular and inferior myocardial infarction.

Patients and methods

PATIENT SELECTION

The computer files of all patients admitted to the MGH MIRU-ISA* for haemodynamic monitoring between January 1969 and July 1977 were searched for patients with a diagnosis of cardiogenic shock in association with inferior myocardial infarction. The diagnosis of cardiogenic shock was based on previously published clinical and haemodynamic criteria (Dunkman *et al.*, 1972; Leinbach *et al.*, 1973). Patients with shock resulting from mechanical lesions (ventricular septal defect, acute mitral regurgitation, tamponade, or cardiac rupture) or rhythm disorders were excluded. Twenty-four patients were identified in the category of inferior myocardial infarction with cardiogenic shock of whom 18 had complete records available for analysis. Six of the 18 patients had haemodynamic evidence of right ventricular dysfunction with a raised right atrial mean pressure equal to or greater than pulmonary artery wedge mean pressure and a right ventricular stroke work index which was less than 2·0 g m per m^2. The records of all 18 patients were reviewed and pertinent clinical, haemodynamic, and electrocardiographic data abstracted and entered on standard forms designed for this study. When available, data from cardiac catheterisation, including coronary arteriography and left ventriculography, and post-mortem examination were also reviewed and included for each patient.

A second group of 27 patients with acute inferior myocardial infarction without shock was also assembled for comparison with the group with inferior myocardial infarction with shock. These patients were selected in the same fashion as the previously described group. All patients in this category had haemodynamic monitoring and complete records were available for analysis in 17 of them. Haemodynamic monitoring was done for one of two reasons: (A) as part of an infarct size reduction study; or (B) to assess treatment for recurrent ischaemia in patients with acute inferior myocardial infarction.

HAEMODYNAMIC DATA

Haemodynamic monitoring was initiated in all patients soon after admission to the MIRU-ISA using previously described techniques (Dunkman *et al.*, 1972). Cardiac output was determined by dye dilution or thermodilution method. In addition to directly measured pressures on the right and left sides of the heart, the following haemodynamic indices were derived using the following formulae:

(A) Cardiac index (CI) = cardiac output/BSA (ml per m^2)

(B) Stroke volume index (SI) = stroke volume/BSA (ml per m^2)

(C) Left ventricular stroke work index (LVSWI) = [systemic arterial mean pressure (MAP) − pulmonary artery wedge mean pressure (PAWP)] × SI × 0·0136 (g m per m^2)

(D) Right ventricular stroke work index (RVSWI) = [pulmonary artery mean pressure (PA) − mean right atrial mean pressure (RA)] × SI ×0·0136 (g m per m^2)

(E) Systemic vascular resistance (SVR) = [(MAP − RA)/cardiac output] × 80 (dynes s cm^{-5})

(F) Pulmonary vascular resistance (PVR) = [(PA − PAWP)/cardiac output] × 80 (dynes s cm^{-5}).

STATISTICAL ANALYSIS

The group means for continuous variables were assessed for significant differences using a computer programme for one way analysis of variance and the Newman-Keuls procedure for multiple comparisons (Snedecor and Cochran, 1967). Discontinuous variables were assessed with the aid of another computer programme for Fischer's exact test. All data are presented as mean ± standard error of the mean (SEM).

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* Massachusetts General Hospital, Myocardial Infarction Research Unit, Intensive Study Area.

Table 1 *Clinical, electrocardiographic, and coronary arteriographic data in patients with inferior myocardial infarction*

	No. of patients	*Mean age (range)*	*History of left ventricular failure*	*Previous anterior myocardial infarction*	*Triple vessel coronary artery disease*	*Hospital mortality*
Cardiogenic shock patients						
With RV dysfunction	6	59 (44–70)*	1*	1*	4/4†	3†
Without RV dysfunction	12	54 (45–66)	3	5	7/8	7
Patients without shock	17	44 (28–64)	0	4	3/12‡	1**

*P = NS vs other groups. †P = NS vs shock patients without right ventricular dysfunction. ‡P < 0·02 vs shock patients with or without right ventricular dysfunction. **P < 0·05 vs shock patients with right ventricular dysfunction; and P < 0·01 vs shock patients without right dysfunction.

Results

CLINICAL, ELECTROCARDIOGRAPHIC, AND CORONARY ARTERIOGRAPHIC DATA

The data for patients with cardiogenic shock both with and without right ventricular dysfunction and for patients without shock are summarised in Table 1. Mean age, past history of left ventricular failure, and electrocardiographic evidence of previous anterior myocardial infarction did not differ significantly in the three groups. The extent of coronary artery disease (defined as reduction in luminal diameter of 50% or more) was known for 12 patients with shock (eight without right ventricular dysfunction and four with right ventricular dysfunction) and 12 patients without shock. In patients with shock, the incidence of triple vessel coronary artery disease was comparable in those patients with and without right ventricular dysfunction but triple vessel disease was significantly less frequent in the patients without shock. Likewise, hospital mortality was comparable in the two groups of patients with cardiogenic shock.

Table 2 *Haemodynamic data in patients with inferior myocardial infarction*

	Pressure (mmHg)			*Stroke work index (g m per m²)*		*Resistance (dynes s cm⁻⁵)*	
Case no.	*Right atrium (mean)*	*Pulmonary artery (mean)*	*Pulmonary artery wedge (mean)*	*Right ventricle*	*Left ventricle*	*Pulmonary vascular*	*Systemic vascular*
Cardiogenic shock patients with right ventricular dysfunction							
1	16	15	10	0·0	16	129	1830
2	15	18	10	0·8	16	156	1070
3	12	16	8	0·7	11	237	1720
4	20	14	11	0·0	32	44	1160
5	9	17	9	1·7	15	206	1830
6	10	14	9	1·1	21	118	1760
Cardiogenic shock patients without right ventricular dysfunction							
7	8	16	11	3·1	23	76	936
8	6	23	13	2·2	5	444	2180
9	8	20	12	3·8	20	246	2060
10	8	13	10	2·4	34	44	1050
11	7	21	14	3·6	15	147	1370
12	8	28	19	2·2	5	424	2820
13	4	30	26	2·7	6	168	3200
14	4	15	8	2·0	11	215	2030
15	13	40	30	5·5	10	276	1810
16	7	24	17	4·6	14	156	1400
17	10	40	27	5·5	10	416	2240
18	7	31	26	6·5	14	129	1940

HAEMODYNAMIC DATA ON ADMISSION

Data for patients with cardiogenic shock with and without right ventricular dysfunction are shown in Table 2. These data were obtained within 24 to 48 hours of the onset of circulatory failure in all patients except one in whom data were obtained approximately 72 hours after the onset of clinical shock. Mean data for the two groups of patients with cardiogenic shock and for the group of patients without shock are given in Table 3.

Patients with shock and right ventricular dysfunction had by definition significantly higher right atrial mean pressure than all other patients. In addition, pulmonary artery and pulmonary artery wedge mean pressures and right ventricular stroke work index were significantly lower in patients with shock and right ventricular dysfunction than in patients with shock but without haemodynamic evidence of right ventricular dysfunction. Furthermore, all patients with right ventricular dysfunction had a wedge pressure 11 mmHg or less compared with only three of 12 patients with shock but without right ventricular dysfunction ($P<0.01$). However, there was no significant difference in left ventricular filling pressure between the six patients with right ventricular dysfunction and the 17 patients without shock. Depression of left ventricular function as assessed by left ventricular stroke work index in patients with shock was similar in those with and without right ventricular dysfunction even though pulmonary artery wedge pressure was significantly lower in the group with right ventricular dysfunction. Systemic vascular resistance was similar in all groups. There was no significant difference in pulmonary vascular resistance between patients without shock and those with shock and right ventricular dysfunction.

RESPONSE TO PLASMA VOLUME EXPANSION

Five of six patients with shock and right ventricular dysfunction were treated initially by plasma volume expansion with salt poor albumin or normal saline, in addition to catecholamine infusions. In three

Table 3 . *Group mean ($\pm$SEM) haemodynamic data*

	Pressure (mmHg)			*Stroke work index (g m per m^2)*		*Resistance (dynes s cm^{-5})*	
	Right atrium (mean)	*Pulmonary artery (mean)*	*Pulmonary artery wedge (mean)*	*Right ventricle*	*Left ventricle*	*Pulmonary vascular*	*Systemic vascular*
Cardiogenic shock patients							
With right ventricular dysfunction	14 ±2*	16 ±1†	10 ±1†	0·7 ±0·3*	18 ±3	148 ±28	1560 ±143
Without right ventricular dysfunction	8 ±1	25 ±3	18 ±2	3·7 ±0·5	14 ±2	228 ±39	1920 ±194
Patients with inferior myocardial infarction without cardiogenic shock	5 ±1	19 ±2	12 ±1	5·9 ±0·7	38 ±3	95 ±11‡	1430 ±167

* $P < 0{\cdot}01$ vs other groups. † $P < 0{\cdot}03$ vs shock patients without right ventricular dysfunction; and P = NS vs patients without shock.
‡ $P < 0{\cdot}01$ vs shock patients without right ventricular dysfunction; and P = NS vs shock patients with right ventricular dysfunction.

patients (cases 1, 2, and 6) there was a rise in pulmonary artery wedge pressure from 9 or 10 mmHg to between 15 and 19 mmHg without any associated rise in cardiac index or decrease in pressor requirements. All three died despite the addition of intra-aortic balloon pumping in two of them (cases 2 and 6). In contrast two other patients (cases 3 and 5) showed a rise in cardiac index from 1·3 to 1·5 and from 1·5 to 2·7 litre/min per m², respectively, in response to plasma volume expansion sufficient to raise wedge pressure from 8 to 17 mmHg in case 3 and from 9 to 14 mmHg in case 5. Intra-aortic balloon pumping was also used in case 5. Both these patients survived. Case 4 also survived with intra-aortic balloon pumping but was not treated by plasma volume expansion.

Five other patients with shock but without evidence of right ventricular dysfunction (cases 7, 9, 10, 14, and 16) also survived. Two (cases 9 and 10) were treated with plasma volume expansion plus catecholamine infusion and did not require intra-aortic balloon pumping. In these two patients fluids were given continuously for 12 to 24 hours after admission. Though wedge pressure did not rise in either patient, cardiac index increased from 1·6 to 2·3 and from 2·8 to 3·1 litre/min per m², respectively. Moreover, the rise in cardiac index in each patient occurred during the time of weaning off and discontinuance of catecholamines. The remaining three surviving patients were treated only with catecholamines and the balloon pump.

NECROPSY FINDINGS

Eight patients, including two (cases 2 and 6) with right ventricular dysfunction, had a post-mortem examination. All the hearts were hypertrophied and in all 40 per cent or more of the left ventricle was infarcted (old plus new) (Fig. 1). Infarction of the posterior interventricular septum was present in both patients with right ventricular functional impairment and in four of six patients without right ventricular dysfunction; the extent of posterior septal involvement was comparable in both groups. Gross evidence of right ventricular infarction was present in case 2, but not in case 6, and extended to the posterior free wall of the right ventricle (Fig. 1). Of patients without evidence of right ventricular dysfunction only case 13 had gross evidence of right ventricular infarction; in this patient, the necrosis was confined to a small basal region of the right ventricular posterior wall.

Microscopical examination of the right ventricle in patients with right ventricular impairment showed multiple and often confluent areas of acute necrosis, primarily involving subendocardial and mid-myocardial zones throughout the right ventricle (Fig. 2). Similar findings in patients with right ventricular infarction have been reported previously (Laurie and Woods, 1963). In contrast, the right ventricle of patients without right ventricular dysfunction (Fig. 3) had no (case 12) or only a few isolated foci of necrosis (cases 13, 17, and 18). In two other patients (cases 11 and 15), right ventricular damage could not be assessed because the relevant sections were not available for review.

Discussion

Several recent studies (Cohn *et al.,* 1974; Rigo *et al.,* 1975; Sharpe *et al.,* 1978; Tobinick *et al.,* 1978) have focused attention on the role of right ventricular infarction when cardiogenic shock is associated with inferior myocardial infarction. In the cases described in these reports the extent of coexistent left ventricular damage has been thought to be modest (Cohn *et al.,* 1974; Rigo *et al.,* 1975). The fact that several of the patients studied have had relatively low pulmonary artery wedge pressures and responded well to fluid administration and/or vasodilator treatment has been taken to support this view. It has therefore been postulated that the occurrence of cardiogenic shock in this situation is the consequence of the inability of the severely damaged right ventricle to pump adequate amounts of blood into the left side of the heart (Cohn *et al.*, 1974; Rigo *et al.*, 1975). This concept is not new and was first proposed by Zaus and Kearns in 1952.

In the present study, however, some observations indicate that in patients with cardiogenic shock in association with combined inferior and right ventricular myocardial infarction, left ventricular damage may be more extensive than has been reported previously. For example, the depression of left ventricular stroke work index in patients with shock was similar in those with and in those without right ventricular infarction. The lower pulmonary artery wedge pressure in patients with right ventricular infarction probably results from right ventricular dysfunction rather than less extensive left ventricular damage. This interpretation is supported by the fact that pulmonary artery wedge pressure was 10 mmHg or less in the two patients with right ventricular infarction studied at necropsy but was 14 mmHg or more (median 26 mmHg) in the six patients without right ventricular dysfunction. Nevertheless, in both groups total extent of infarction (old plus new) was 40 per cent or more of the left ventricular myocardium.

Further, despite initial wedge pressures of 11 mmHg or less in all patients with haemodynamic evidence of right ventricular infarction, only two of five treated by plasma volume expansion responded with an increase in cardiac index and both survived. In contrast, the remaining three patients all raised their wedge pressure to 'optimal' levels (Crexelis *et al.*, 1973) and yet all three failed to increase the cardiac index and all subsequently died. The fact that the non-survivors showed a rise in left ventricular filling pressure with no increase in cardiac index suggests that the left ventricle in these patients was functioning on the flat portion of a depressed Starling curve, and therefore failed to respond to plasma volume expansion. It appears, therefore, that patients with right ventricular infarction and cardiogenic shock can be subdivided into at least two groups: in one group very severe left ventricular damage is usually incompatible with survival; in another group, there is less severe left ventricular damage and sufficient viable myocardium to permit them to respond favourably to plasma volume expansion and to other treatment. However, because of right ventricular dysfunction, both groups may have relatively low left-sided filling pressures.

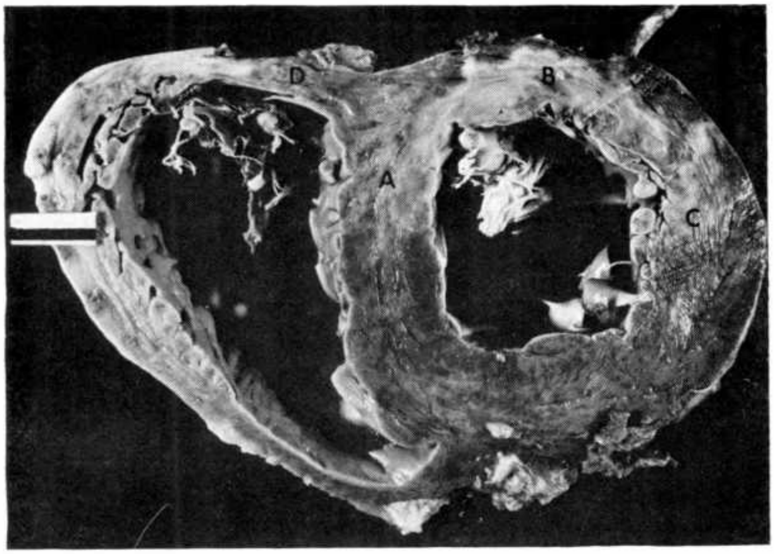

Fig. 1 *Post-mortem section of heart from case 2. There is recent infarction involving posterior septum* (A), *posterior wall* (B), *and lateral wall* (C) *of left ventricle. In addition, posterior wall of right ventricle* (D) *is involved by recent infarction. The remainder of the right ventricular free wall appears grossly uninvolved by infarction. Total left ventricular necrosis totalled 40 per cent.*

These findings have a number of implications for the management of patients with cardiogenic shock and right ventricular infarction. Thus, if plasma volume expansion is used in an attempt to relieve circulatory failure, close attention should be directed toward the response of left ventricular stroke work to an increase in pulmonary artery wedge pressure induced by the increased plasma volume. It is possible that these patients may have more left ventricular damage than their initial wedge pressures suggest and thus may not respond favourably to volume loading. This was the case in three of five patients with right ventricular infarction in this series. Likewise, if vasodilators are used then agents that work predominantly on the arterial side of the circulation may be the most appropriate choice since excessive venodilatation and consequent preload reduction may have an adverse effect in this situation. In addition, in view of the frequent occurrence of severe left ventricular damage, early consideration of intra-aortic balloon pumping also appears warranted (Leinbach *et al.*, 1978). Finally, because the distinction of those patients with very severe left ventricular damage

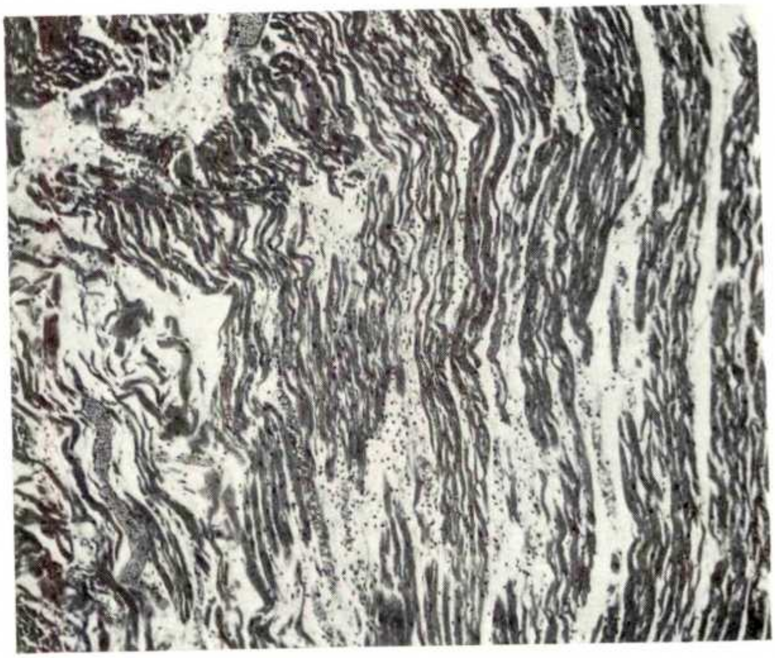

Fig. 2 *Photomicrograph of representative section of lateral right ventricular wall from case 2 shows extensive necrosis of myocytes and early infiltration by polymorphonuculear leucocytes. (H. and E. ×80.)*

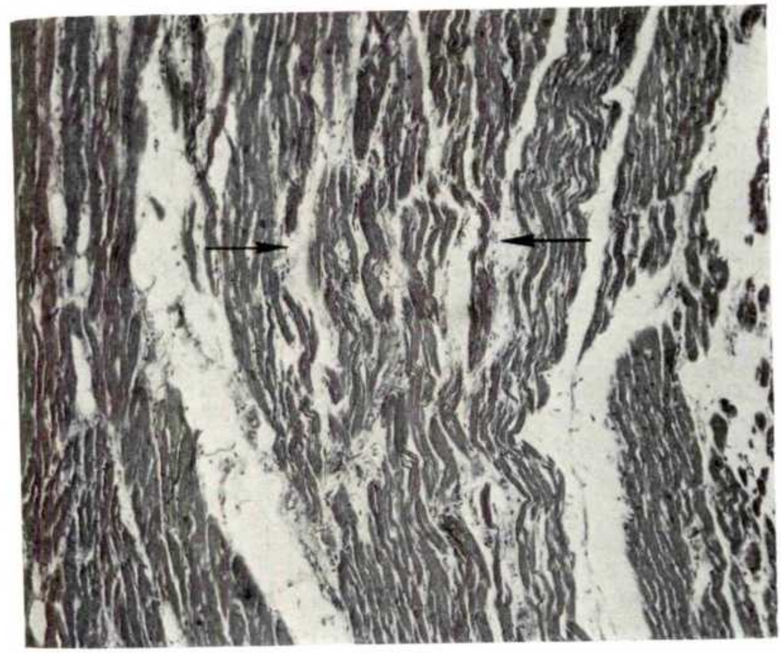

Fig. 3 *Photomicrograph of representative section of right ventricle from case 17, without haemodynamic evidence of right ventricular dysfunction. Only isolated foci of myocyte necrosis* (arrows) *are present. (H. and E. ×80.)*

from those with less severe damage may be impossible from haemodynamic observations alone, it may be useful to obtain radionuclide ventriculograms in these patients in order to make this important distinction (Rigo *et al.*, 1974).

In summary, the present study indicates that when cardiogenic shock is associated with combined right ventricular and inferior myocardial infarction, this may be associated with more severe left ventricular damage than has previously been reported. Furthermore, right ventricular dysfunction in this situation may cause relatively low left-sided filling pressures even in the presence of extensive left ventricular infarction. This may be a cause of error in the clinical and haemodynamic assessment of the extent of left ventricular damage present. Since the extent of left ventricular damage will ultimately not only determine the response to treatment but also prognosis (Sobel *et al.*, 1972; Weber *et al.*, 1978), it is clearly important to attempt to distinguish those patients with very severe left ventricular infarction from those in whom left ventricular damage is less extensive. Radionuclide ventriculograms may prove useful for this purpose and should, therefore, be obtained as early as possible in the patient's illness.

We wish to acknowledge the IDH-SCOR Data Management Center for expert assistance with the statistical analysis of the data.

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Evaluation of praecordial ST segment mapping as an index of infarct size in patients with acute myocardial infarction[1]

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SUMMARY We evaluated the usefulness and limitations of praecordial ST segment mapping as a clinical means of assessing the size of acute myocardial infarction in 14 patients with anterior myocardial infarction and 13 patients with inferior myocardial infarction. ΣST, the sum of ST segment elevations, and nST, the number of leads showing ST segment elevation, were obtained from serial electrocardiograms recorded through 39 praecordial leads. The infarct size and period of the evolution of myocardial infarction were estimated respectively from the total creatine kinase (CK) released and the serial changes of the CK releasing rate. ΣST and nST obtained at the time when the CK release had ceased correlated closely with the total CK released. Peak ΣST and nST, and values 48 hours after the onset of myocardial infarction, also correlated well with the total CK released; but those on admission or 12 hours after the onset correlated poorly.

These results suggest that ΣST and nST at the end of evolution of myocardial infarction or 48 hours after the onset may be two useful indices for the assessment of infarct size in patients with either anterior or inferior myocardial infarction.

Many attempts (Maroko *et al.*, 1972; Norris *et al.*, 1975; Henning *et al.*, 1978; Sharpe *et al.*, 1978) have been made to assess infarct size in patients with acute myocardial infarction, because the extent of necrosis directly influences cardiac function and subsequent prognosis (Page *et al.*, 1971; Sobel *et al.*, 1972; Mathey *et al.*, 1974; Hori *et al.*, 1979). Maroko *et al.* (1971) reported a close correlation between the magnitude of epicardial ST segment elevation 15 minutes after experimental coronary occlusion in dogs, and infarct size as determined by loss of myocardial creatine kinase (CK) activity or as determined histologically 24 hours later. Their further study (Muller *et al.*, 1975) also showed that in dogs the magnitude of epicardial ST segment elevation correlated well with that of praecordial ST segment elevation. Though it is now widely recognised that surface mapping of the electrocardiogram is useful in evaluating the effect of therapeutic interventions on the extent of infarction, the usefulness of this technique in measuring human infarct size remains controversial (Reese *et al.*, 1973; Norris *et al.*, 1976; Thompson and Katavitis, 1976) perhaps because serial changes of ST segment elevation after the onset of infarction have been studied inadequately. In this study we attempted to investigate the serial changes in the praecordial ST segments to evaluate the feasibility of the surface mapping technique as an index of infarct size both in patients with anterior infarction and with inferior infarction.

Subjects and methods

Of 34 consecutive patients with acute myocardial infarction who were admitted to the Coronary Care Unit of Sakurabashi Watanabe Hospital within 12 hours after the onset of infarction, 27 were studied. We excluded two patients with previous myocardial infarction, three patients whose infarct size could not be assessed because of early death, and two patients with intraventricular conduction delay. None of the 27 patients in our series had pericarditis or a cerebrovascular accident which might influence

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ST segment changes. Fourteen patients had anterior infarction (13 men and one woman, ages 33 to 77, with a mean of 53 years). This group included one patient with lateral infarction and another with dominantly subendocardial infarction and only partial transmural anterior infarction; these two were excluded from the statistical analysis. Thirteen patients had inferior infarction (eight men and five women, ages 44 to 82 years, with a mean of 66 years). The diagnosis was made by a typical history, characteristic alterations of ST-T wave changes on the standard 12 lead electrocardiograms, and diagnostic rise and fall in serum enzymes (creatine kinase, α-hydroxybutyric dehydrogenase, aspartate aminotransferase, and lactic dehydrogenase).

(1) PRAECORDIAL ST SEGMENT MAPPING TECHNIQUE

Electrocardiograms were recorded through unipolar leads ('V' lead) from 39 points, which were marked with an indelible pen so that all subsequent recordings were obtained from the same points. The 39 points comprised 21 points on the anterior chest and 18 points on the left lateral chest as shown in Fig. 1.

Electrocardiograms were recorded, using a thermal pen recorder on standard electrocardiographic paper running at 25 mm/s with standardisation of 1 mV/cm, on admission and 12, 24, 36, 48, 72 hours, and seven and 14 days after the onset of chest pain. Whenever possible, electrocardiograms were also obtained three and six hours after the onset of pain. The magnitude of ST segment elevation of recorded electrocardiograms was measured at the J point to the nearest 0·5 mm.

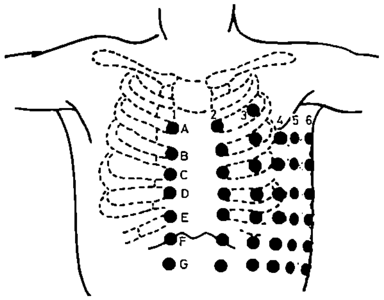

Fig. 1 *The positions of 39 praecordial leads. Twenty-one points on the anterior chest were at the intersections of three imaginary vertical lines (1: right sternal border; 2: left sternal border; 3: left mid-clavicular line) and seven horizontal lines (A–E: second to sixth intercostal space near the sternum; F: 2·5 cm below E; G: 2·5 cm below F). Eighteen points on the left lateral chest were at the intersections of three vertical lines (4: anterior axillary line; 5: mid-axillary line; 6: posterior axillary line) and six horizontal lines (B to G as above).*

The sum of ST segment elevations from all leads (ΣST) and the number of leads showing ST segment elevation of 0·5 mm or greater (nST) were calculated from each recording.

In order to evaluate the reproducibility of measured ST segment elevation, the praecordial ST segment mapping was recorded again one hour after we recorded the three-hour or the 48-hour electrocardiograms in 10 patients. Two cardiologists independently measured ST segment deviation in each electrocardiogram recorded from five patients to assess the variation among observers.

(2) ASSESSMENT OF INFARCT SIZE BY TOTAL CK RELEASED (ΣCK)

Venous blood samples for CK determination were obtained at four-hour intervals from the time of admission until serum enzyme levels returned to normal. The appearance function of CK released from the infarcted myocardium was calculated by the method of Sobel *et al.* (1972) as modified by Norris *et al.* (1975) and used as a guide in assessing the time course of evolution of the infarct (Inoue *et al.*, 1977). Total CK released (ΣCK) was measured by integrating this appearance function and was used as an index of infarct size. Total CK released up to 24 and 48 hours after the onset, ΣCK_{24} or ΣCK_{48}, respectively, were also measured in order to compare the change in ΣST from 24 to 48 hours. Though the evolution of the infarct was considered to cease at the time when the appearance function of CK released became zero IU/ml per h (Inoue *et al.*, 1977), the exact determination of this time was difficult because it could be influenced substantially by subtle alterations in the disappearance rate of serum CK activity. Therefore, in this study the time when the appearance function decreased to 5 IU/ml per h was regarded as the end point of evolution; this time is much less influenced by the alteration in the disappearance rate of serum CK activity. In practice, ΣST and nST at the end of evolution were obtained by linear interpolation of the two values which were measured at the closest points immediately before and after the time when the appearance function became 5 IU/ml per h or less.

Results

(A) EVALUATION OF ST SEGMENT MAPPING AS AN INDEX OF INFARCT SIZE

(1) *Serial changes in ΣST and nST*

ΣST and nST were obtained on admission and 12, 24, 36, 48, and 72 hours, and on the seventh and 14th day after the onset in all patients studied. ΣST and nST were also obtained three and six hours after the onset in six and 17 patients, respectively. Fig. 2 and 3 show the serial changes in ΣST and nST in patients with anterior and inferior infarction. The data three hours after the onset in patients with inferior infarction are not depicted in Fig. 3 since they were obtained in only two patients. Serial changes in ΣST, nST, and the appearance function of CK in two representative cases are shown on the same time scale in Fig. 4 and 5.

In one case with anterior infarction shown in Fig. 4, ΣST and nST increased to their peaks 48 hours and 24 hours after the onset, respectively, and then decreased gradually. In contrast, another case with anterior infarction showed a typical biphasic pattern of ΣST and nST as shown in Fig. 5; both indices showed a transient decrease between six and 12 hours after the onset of infarction and then increased again without any important changes in blood pressure, heart rate, or symptoms. Such a biphasic pattern was observed in six out of 12 patients (50%) with anterior infarction and eight out of 13 patients (62%) with inferior infarction. It was of great interest, however, that in almost all patients both ΣST and nST reached a somewhat stable state at the end of evolution of infarction judged from the appearance function of CK released (see Methods) and showed a gradual decrease thereafter, as shown in Fig. 4 and 5.

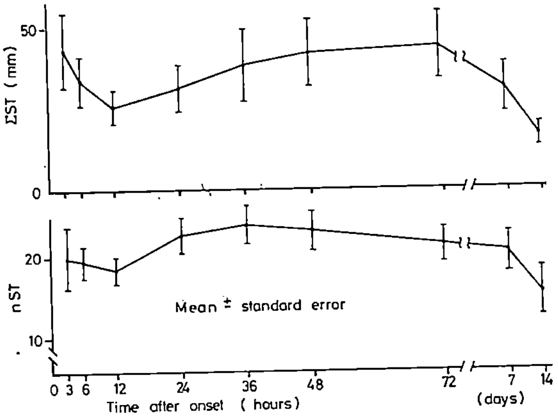

Fig. 2 *The time course of mean values of ΣST* (upper panel) *and nST* (lower panel) *after the onset in 12 patients with anterior infarction. ΣST and nST three and six hours after the onset were obtained in four and nine patients, respectively.*

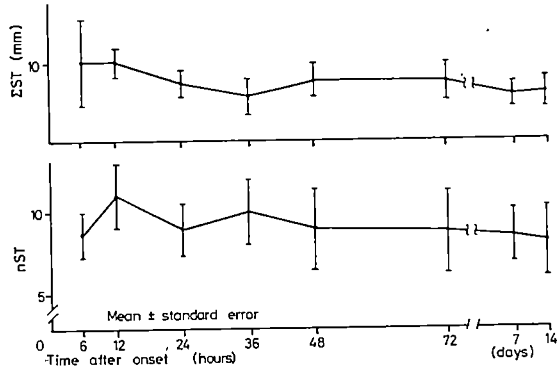

Fig. 3 *The time course of mean values of ΣST* (upper panel) *and nST* (lower panel) *after the onset in 13 patients with inferior infarction. These indices six hours after the onset were obtained in eight patients. The data three hours after the onset were not depicted since they were obtained in only two patients.*

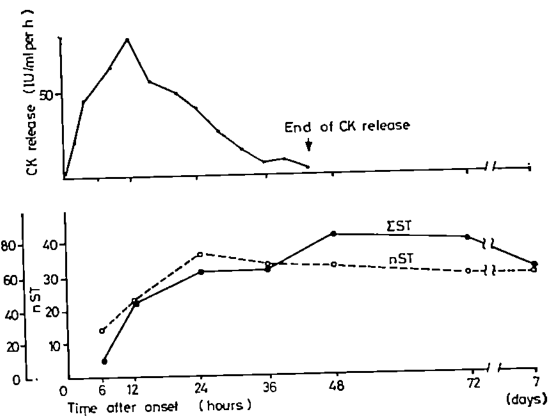

Fig. 4 *Serial changes in CK release per hour* (upper panel), *ΣST and nST* (lower panel) *in a representative case with anterior infarction.*

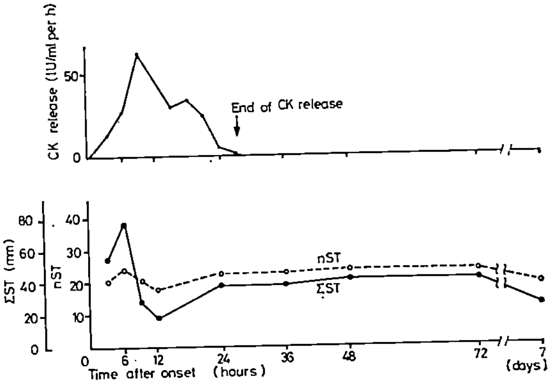

Fig. 5 *Serial changes in CK release per hour* (upper panel), *ΣST and nST* (lower panel) *in a representative case with anterior infarction.*

(2) *ΣST and nST at end of evolution of infarction*

The mean values of ΣST and nST at the end of evolution of infarction (henceforth designated as ΣST_{end} and nST_{end}, respectively) and the duration of evolution (the duration of CK release) are shown in Table 1. It was seen that ΣST_{end} andn ST_{end} correlated closely with the total CK released, which represents the infarct size in 12 patients with anterior infarction (ΣST: $r = 0{\cdot}82$, $P < 0{\cdot}01$;nST: $r = 0{\cdot}85$, $P < 0{\cdot}01$, see Fig. 6). Values from two patients who were excluded from the statistical analysis (one with lateral infarction and another with subendocardial infarction and only partial transmural anterior infarction) were also plotted in Fig. 6; they were far below the regression line, indicating that these ΣST and nST were disproportionately too small in comparison with the infarct size estimated enzymatically. In 13 patients with inferior infarction there was also a significant correlation between ΣST_{end} and nST_{end} and infarct size (ΣCK) (ΣST_{end}: $r = 0{\cdot}84$, $P < 0{\cdot}01$; nST_{end}: $r = 0{\cdot}72$, $P < 0{\cdot}01$, see Fig. 7). These results strongly suggest that ΣST and nST at the end of the evolution of infarction directly reflect infarct size in both anterior infarction and inferior infarction, but not for lateral or subendocardial infarction.

Table 1 *Mean values of ΣST and nST at end of evolution of infarct and duration of evolution in patients with anterior and inferior infarction*

	Number of cases	*ΣST_{end} (SEM) (mm)*	*nST_{end} (SEM)*	*Duration of evolution (SEM) (h)*
Anterior myocardial infarction	n = 14	35·3 ± 7·3	21·5 ± 2·2	38·7 ± 4·7
Inferior myocardial infarction	n = 13	10·2 ± 2·0	11·0 ± 1·6	41·0 ± 3·7

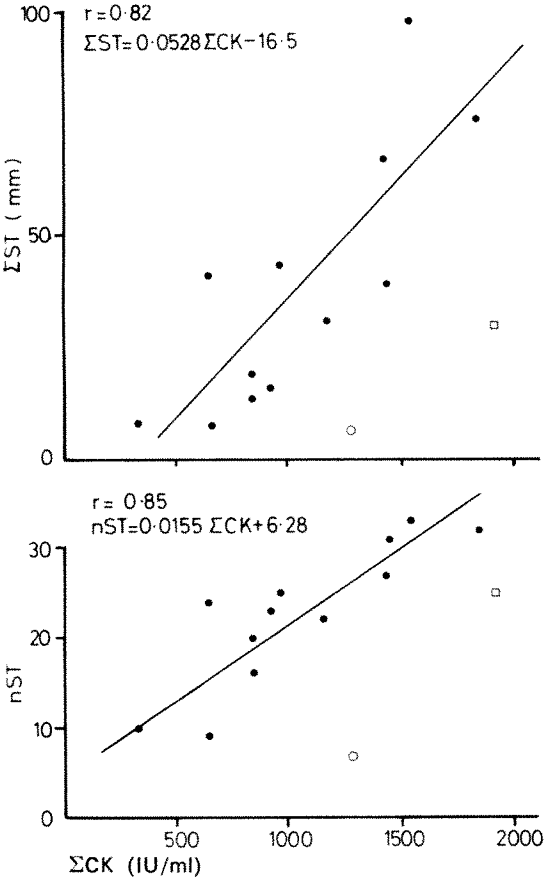

Fig. 6 *Relations between ΣST* (upper panel), *nST* (lower panel), *and the total CK released (ΣCK) at the end of evolution of anterior infarction.* ☐ *: a case with ateral infarction;* ○ *: a case with subendocardial infarction and partial transmural anterior infarction.*

(3) *ΣST and nST 48 hours after onset of infarction*
Since in 80 per cent of all patients the evolution of infarction had ceased within 48 hours after the onset of chest pain, the relation between ΣST and nST 48 hours after the onset (designated as ΣST_{48} and nST_{48}, respectively) and infarct size (ΣCK)

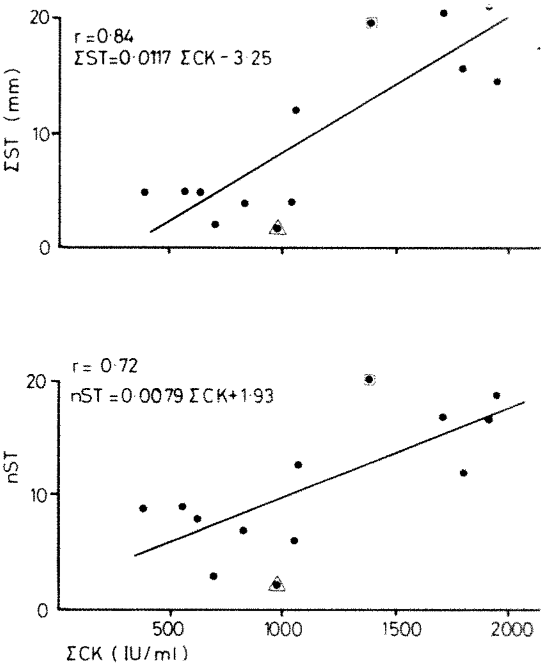

Fig. 7 *Relations between ΣST* (upper panel), *nST* (lower panel), *and the total CK released (ΣCK) at the end of evolution of inferior infarction.* ⊡ *: a case with inferoseptal infarction;* ▲ *: case with inferoposterior infarction.*

was also investigated. We found that ΣST_{48} and nST_{48} also correlated significantly with ΣCK in both anterior infarction and inferior infarction; r=0·72 (P<0·01) for ΣST_{48} and r=0·77 (P<0·01) for nST_{48} in anterior infarction and r=0·86 (P<0·01) for ΣST_{48} and r=0·66 (P<0·01) for nST_{48} in inferior infarction (see Table 2).

Table 2 *Correlations between ΣST and/or nST and total CK released (ΣCK) at various time intervals after onset of infarction*

	Anterior infarction		*Inferior infarction*	
	ΣST	*nST*	*ΣST*	*nST*
On admission ($\Sigma ST_{\text{initial}}$, nST_{initial})	0·43	0·67*	0·63*	0·53
At 12 h after onset (ΣST_{12}, nST_{12})	0·58	0·58	0·74†	0·55
At 48 h after onset (ΣST_{48}, nST_{48})	0·72†	0·77†	0·86†	0·66†
At peak time ($\Sigma ST_{\max}$, $nST_{\max}$)	0·76†	0·86†	0·79†	0·68†
At end of evolution (ΣST_{end}, nST_{end})	0·82†	0·85†	0·84†	0·72†

*P<0·05. †P<0·01.

(4) *ΣST and nST at their peaks*

In our series maximal ΣST and nST were obtained at 38·3±7·0 (SEM) hours and 33·3±5·8 (SEM) hours, respectively, in patients with anterior infarction, and 31·9±6·3 (SEM) hours and 25·9±4·3 (SEM) hours, respectively, in patients with inferior infarction. The maximal ΣST and nST (henceforth designated as $\Sigma ST_{\max}$ and $nST_{\max}$) also correlated significantly with the infarct size (ΣCK): r=0·76 (P<0·01) for $\Sigma ST_{\max}$ and r=0·86 (P<0·01) for $nST_{\max}$ in anterior infarction, and r=0·79 (P<0·01) for $\Sigma ST_{\max}$ and r=0·68 (P<0·01) for $nST_{\max}$ in inferior infarction.

(5) *ΣST and nST on admission and 12 hours after onset of infarction*

ΣST and nST on admission ($\Sigma ST_{\text{initial}}$ and nST_{initial}) and 12 hours after the onset (ΣST_{12} and nST_{12}) were found to be poorly correlated with total CK released (especially $\Sigma ST_{\text{initial}}$) in anterior infarction (r=0·43, P>0·05) and nST_{initial} in inferior infarction (r=0·53, P>0·05, see Table 2). These results strongly suggest that ΣST and nST during the early phase of the progression of infarction do not directly reflect the extent and severity of tissue necrosis of the myocardium.

(6) *Detection of extension of infarction by serial change of ΣST or nST*

To investigate whether the serial change of ΣST or nST can directly reflect the instantaneous evolution of infarct, the change of ΣST or nST between 24 and 48 hours after the onset was compared with the amount of increase in CK released during this interval (ΣCK_{24} to ΣCK_{48}). In five of 11 patients (45·5%) with anterior infarction and nine of 13 patients (69%) with inferior infarction, ΣST increased with the increase in ΣCK, shown by arrows in the right upper part of Fig. 8. One patient with anterior infarction was excluded because the electrocardiogram recorded 24 hours after the onset showed transient right bundle-branch block. In this figure, however, some arrows point downwards, indicating that ΣST decreased from 24 to 48 hours after the onset of infarction. This suggests that ΣST decreases in some patients despite the evolution of infarct. This was also true of nST.

In summary, our results indicate that the infarct size in patients both with anterior infarction and with inferior infarction may be estimated by ΣST and nST obtained from the praecordial electrocardiographic mapping at the time when the

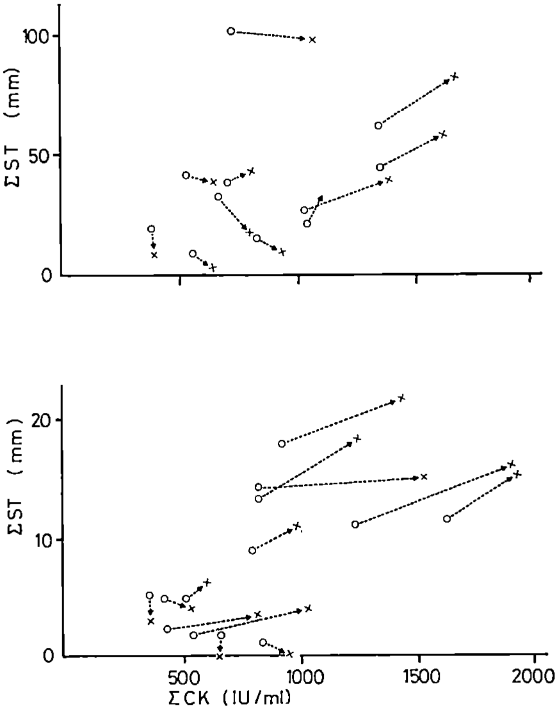

Fig. 8 *Individual changes in ΣST relating to the changes in ΣCK till the corresponding time to ΣST in 11 patients with anterior infarction* (upper panel) *and in 13 patients with inferior infarction* (lower panel). *Open circle and cross mark represent the data obtained 24 and 48 hours after the onset, respectively. Dashed arrow represents the direction of change from 24 to 48 hours after the onset.*

evolution of infarct has ceased (ΣST_{end} and nST_{end}) or 48 hours after the onset, when the evolution is considered to have been completed in most of the cases (ΣST_{48} and nST_{48}). ΣST and nST at these times after the onset closely correlated with infarct size (ΣCK), probably because ST segment elevation becomes stable after evolution of the infarct has ceased, and the ischaemic injury zone would be proportional to the extent of tissue necrosis at this stage of the disease. In contrast, however, at the early stage during the evolution of the infarct, praecordial ST segment elevation does not reflect the infarct size. Thus, ΣST and nST 12 and 24 hours after the onset correlated poorly with ΣCK, probably because the surrounding ischaemic zone is labile and greatly influenced by small alterations in coronary blood supply and oxygen demand during evolution of the infarct.

(B) REPRODUCIBILITY OF ST SEGMENT MAPPING TECHNIQUE

The variation in measurement of ST segment displacement was 7·6 ±8·3 per cent (mean ±SD) in 25 recordings obtained from five patients, indicating that errors from this source are small. Though the hour-to-hour variation about three hours after the onset was 26·7 ±8·9 per cent (mean ±SD) in five patients, the variation about 48 hours after onset was 3·5 ±2·6 per cent (mean ±SD) in five patients.

These results suggest that ΣST obtained about 48 hours after the onset is stable enough to be meaningful.

Discussion

In this study we evaluated the validity of praecordial ST segment mapping and also its limitation as an index of infarct size in patients both with anterior infarction and with inferior infarction. The sum of the magnitude of ST segment elevations (ΣST) and the total number of leads showing ST segment elevation (nST) during the early phase of infarction, within 12 hours after the onset, did not accurately reflect the extent of infarction. However, ΣST and/or nST measured at the time when the evolution of infarct had ceased or the maximal ΣST and/or nST did closely correlate with infarct size. This method may be useful in patients with inferior as well as anterior infarction.

Since Maroko *et al.* (1971) established epicardial ST segment mapping as a method for the assessment of infarct size, it has been predicted that praecordial ST segment mapping would also be useful clinically to evaluate the effect of therapeutic interventions during the course of acute myocardial infarction and also to detect the extension of infarction. However, the validity of quantification of praecordial ST segment elevation for the assessment of infarct size has remained controversial. Norris *et al.* (1976) reported that there was no significant correlation between the peak value of ΣST and the infarct size estimated by the same method in our study. Thompson and Katavitis (1976) also showed the clinical limitation of this method; only a rough correlation ($r=0{\cdot}48$, $n=12$) was found between ST segment elevation and infarct size (ΣCK), and in some cases the extension of infarction could not be detected with this technique.

In evaluating the quantification of ST segment elevation, however, the factors influencing the deviation of the ST segment on the praecordial leads must be taken into account. Though the origin of ST segment elevation, that is ischaemic injury current, is believed to be derived from the potential gradient across the boundary of ischaemia resulting from the alteration in action potential, electrical potential recorded on the chest surface can be influenced by other factors, for example the solid angle of the ischaemic zone subtended at a point of the electrode, and electrical conductivity of the tissues between the ischaemic zone and the electrode on the chest surface. Indeed, these factors which greatly influence underlying ischaemic potential gradient are of great importance in the interpretation of ST segment deviations in surface electrocardiograms, because the extent of infarction as well as the site of infarction directly influence the solid angle of the ischaemic area subtended at a point of the electrode. Even if individual variations in the potential gradient across the boundary of the ischaemic area and electrical conductivity of the thorax were both negligibly small, the difference in infarct site would greatly distort the distribution of ST segment elevation. In fact, in our study the regression lines indicating a significant correlation between ΣST or nST and infarct size (ΣCK) in anterior infarction were quite different from those in inferior infarction. Moreover, in two patients who were excluded from the statistical analysis, one with lateral infarction and another with subendocardial infarction and only partial transmural anterior infarction, both ΣST and nST deviated downward from the regression line (see Fig. 6), indicating that in these cases the solid angle, which is proportional to ST segment elevation, was disproportionately small for the infarct size.

Similarly, infarct site can influence ST segment elevation in patients with inferior infarction. Indeed, there were two patients with inferior infarction like those with anterior infarction whose ΣST and nST substantially deviated from the regression line (see Fig. 7). Of these patients, one had an infarct extending towards the septal wall showing that ΣST and nST deviate upward from the regression line (Fig. 7). The other had an infarct extending toward the posterior wall, with downward deviation of ΣST and nST from the regression line (Fig. 7). In the former, the ST segment elevation caused by septal infarction might be superimposed on that of inferior infarction; while, in the latter, the reciprocal ST segment depression caused by posterior infarction may offset the underlying ST segment elevation. These results strongly suggest that both infarct site and infarct size are major factors which should be taken into account when we evaluate the ST segment elevation. In this study, apart from the patients with infarction extending toward other regions than the anterior or inferior wall and also in subendocardial infarction, the ΣST and nST correlated closely with the infarct size in patients both with anterior and with inferior infarction.

The present study showed that the time course of ST segment change was of great importance in assessing infarct size. Since the variation of measurement was so small as to be neglected (observation variation: 7·6 ±8·3% and hour-to-hour variation 48 hours after the onset: 3·5 ±2·6%), changes in ST segment elevation should reflect the change in extent and/or severity of ischaemia even though changes in electrical conductivity of the thorax such as that resulting from pulmonary oedema would also contribute to ST segment change to some extent. However, the extent of the ischaemic area may not be proportional to that of tissue necrosis, especially during the acute phase of infarction. Cox *et al.* (1968) showed that in experimental dogs the size of myocardial ischaemia reached its maximum 18 hours after ligation of a coronary artery, while that of myocardial necrosis reached its maximum several hours later than that of ischaemia. These findings agree with our present observation: ST segment elevation which should represent the extent and/or severity of ischaemia became maximal on average 35·2 hours after the onset of chest pain, while the duration of CK release, which represents the evolution of tissue necrosis, was on average about 40 hours.

The discrepancy of evolution between ischaemia and necrosis may be substantially large in the early phase of infarction because in this phase the regional oxygen balance is easily influenced by haemodynamic changes. Indeed, in more than 50 per cent of patients, ΣST and nST decreased a day after the onset while CK release continued. This discrepancy between the extent of ischaemia and necrosis size would account for poor correlation between ΣST or nST and infarct size (ΣCK) on admission and 12 hours after the onset of infarct. In contrast, ST segment elevation around the end of the evolution of infarct correlated highly with infarct size (Fig. 6 and 7). This finding indicates that at this stage the surrounding ischaemic area has already been established in proportion to infarct area.

Morris *et al.* (1974) also reported that the degree of ST segment displacement at 48 hours of infarction was related to the mean maximum serum AST (GOT) activity. This report agrees with our results. Poor or absent correlation between ΣST and infarct size (ΣCK) observed by Norris *et al.* (1976), and Thompson and Katavitis (1976) might have resulted because they measured ΣST long before the end of the evolution of infarction. The variation in infarct site in their studies might also account for poor correlation.

Although ΣST or nST at the end of the progression of the infarct or the maximal ΣST or nST can represent infarct size, the determination of these indices is difficult in patients who are not admitted immediately after the onset, and when enzymatic assessment of infarct size is not available. In such cases, praecordial ST segment mapping 48 hours after the onset could be of value in assessing infarct size.

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Haemangioendotheliosarcoma of the heart
Diagnosis and treatment

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SUMMARY A case of haemangioendotheliosarcoma of the right atrium in a 28-year-old man is reported. The presence of a continuous murmur to the right of the sternum as a clue to the diagnosis is pointed out, and the usefulness of cardiac catheterisation and angiography in making diagnosis emphasised. Irradiation therapy with cobalt-60 had a palliative effect upon this malignant tumour.

Although only about 60 cases of primary cardiac haemangioendotheliosarcoma have been described, it is, together with rhabdomyosarcoma, the most frequent malignant primary tumour of the heart (Gröntoft and Hellquist, 1977). The clinical picture in the published cases has tended to uniformity, but without specific clues to the diagnosis—a malignant primary cardiac tumour was suspected during life in only 13 of these patients and in only 8 was the diagnosis of haemangioendotheliosarcoma established before death. Three of these received irradiation therapy, with varying results. In the remaining patients the average survival time from the onset of symptoms was approximately 6 months.

Our patient is of special interest as clinical signs and findings at cardiac catheterisation enabled a presumptive diagnosis of a malignant angiomatous tumour in the right atrium to be made. This diagnosis was subsequently confirmed at operation.

The effect of irradiation and chemotherapy was evaluated at an advanced stage of the disease.

Case report

A 28-year-old man was in good health until November 1975, when he developed fever, cough, and a sore throat. He was given penicillin without improvement.

In February 1976, he was seen by a cardiologist after a chest x-ray film had shown slight cardiac enlargement. A friction rub was heard over the heart and because of a raised antistreptolysin O titre, rheumatic fever was suspected. Treatment with phenoxillin was started but he failed to improve, complaining of fatigue and dyspnoea.

In October 1976, he was admitted to our department after an episode of haemoptysis. On examination there was no jugular venous congestion. The only remarkable finding was a continuous murmur (grade 2-3/6) maximal in the fifth and sixth intercostal spaces approximately 4 cm to the right of the sternum. The murmur was unaffected by respiration and body position, and it was inaudible in the classical sites of auscultation. There was a split second sound with an accentuated pulmonary component. The electrocardiogram was normal and remained so thereafter. The chest x-ray showed that the heart was moderately enlarged, with a bulging and slightly irregular right cardiac border. In both lung fields small scattered infiltrates were seen. Urinanalysis, routine haematology and biochemistry, ESR, liver function studies, serum protein electrophoresis, and various serological tests for viral and fungal infection were all normal. There were no lupus erythematosus cells and cultures for tuberculosis from the sputum and gastric aspirate were negative. Bronchoscopy revealed blood in the bronchial tree, but no tumour tissue was seen in biopsy material.

Right-sided cardiac catheterisation (Table) disclosed normal pressures and cardiac index, but the oxygen saturation showed a small but consistent step-up between the venae cavae and the pulmonary artery with the main increase at right ventricular level, suggesting a left to right shunt. Catheter manoeuvrability suggested an abnormality in the

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Table *Cardiac catheterisation*

Site	*Pressure (mm Hg)*	*Oxygen saturation (% O_2)*		
Superior vena cava		64	63	60
Inferior vena cava		60	59	
Right atrium	11/5	63	66	66
Right ventricle	26/10	73	71	71
Pulmonary artery	26/12	72	73	69
Pulmonary wedge	12	100		
Cardiac index	2·6 l/min per m²			

lower part of the right atrium and a biplane angiocardiogram confirmed the presence of a tumour bulging into its cavity and compressing the superior vena cava (Fig. 1).

The continuous murmur, the left-to-right shunt, and the filling defect in the right atrium suggested an angiomatous tumour in the right atrium also probably infiltrating the right ventricle.

In December 1976, the heart was exposed through a median thoracotomy and the diagnosis of a haemangioendotheliosarcoma confirmed by biopsy. The tumour was deemed inoperable as several metastases were seen in the left lung. Postoperatively the patient was very dyspnoeic and needed continuous oxygen therapy. He was irradiated with cobalt-60 to a total of 3000 rad, and then given chemotherapy (lomustine, doxorubicin, vinblastine, and prednisone). Over the next 2 months he improved sufficiently to be discharged but in April 1977, bronchopneumonia developed and he died 17 months after the initial symptoms.

PATHOLOGY

Necropsy, gross

The pericardium was adherent to the surroundings and contained no fluid.

The heart weighed 630 g (1·3% of the total body weight) and measured 10 × 11 cm. The right atrium was enlarged and had several dark tumour nodules on the surface, the largest being 1·2 cm in diameter (Fig. 2a). The wall of the right atrium was greatly thickened and firm (Fig. 2b), the colour varying from grey-yellow to dark red. The tumour occupied two-thirds of the right atrial wall and continued from the orifice of the superior vena cava into the epicardial tissue surrounding the right coronary artery.

Numerous metastases were found in both lungs and two in the liver; they were all red and full of blood.

Microscopy

All sections were stained by H+E, elastic van Gieson, PTAH, reticulin stain, and Masson's trichrome method. Sections from the right atrial wall and the upper part of the anterior wall of the right

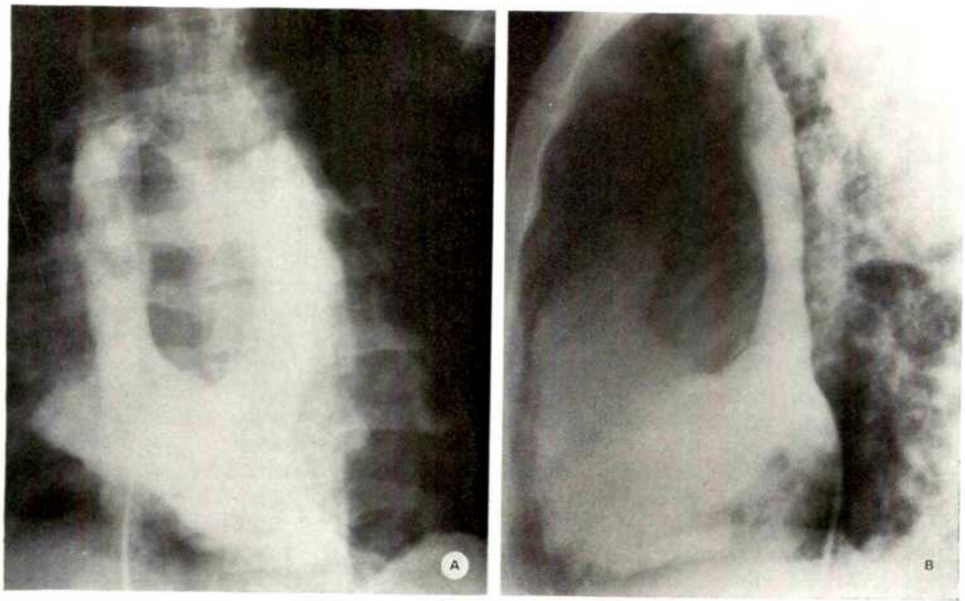

Fig. 1 *Biplane angiocardiography. (A) Frontal projection. (B) Lateral projection. Films selected from serial studies made after injection in the right atrium. There is opacification of the superior vena cava, the right atrium, the right ventricle, and the pulmonary artery. The right atrium is seen to be the site of a large irregular filling defect.*

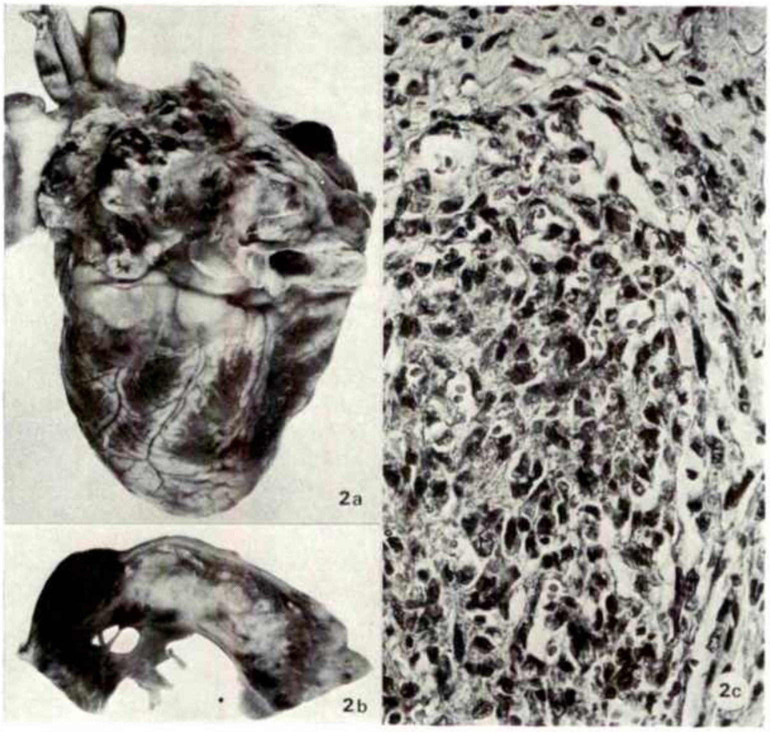

Fig. 2 *(a) Posterior aspect of the heart. Large tumour nodules are seen at the top right. (b) Section from the right atrium through the largest tumour nodule (real size). (c) Section from the tumour tissue. Erythrocytes are seen in several of the irregular channels lined by malignantly transformed endothelium. (H + E. × 330.)*

ventricle showed diffuse tumour growth, haemorrhage, necrosis, and fibrosis. The tissue was solid in some areas, but irregular clefts and channels containing erythrocytes were seen in many parts, lined by coarse and pleomorphic endothelial cells. The nuclei were often spindle shaped, hyperchromatic, and enlarged; 1 to 2 nucleoli were frequently seen (Fig. 2c). The appearances were consistent with haemangioendotheliosarcoma.

Discussion

Haemangioendotheliosarcoma of the heart occurs almost exclusively in the right atrium and produces either haemorrhagic pericardial effusion or inflow obstruction of the right side of the heart (Glancy *et al.*, 1968). In only 3 patients has the tumour been located solely in the left atrium (Penneman, 1908; Gross and Englehart, 1937; Hager *et al.*, 1970).

The lack of a specific clinical picture has made diagnosis in life difficult. In at least 7 of the reported patients tuberculosis was suspected (Kauder and Müller, 1968; Freeland *et al.*, 1971; Tse and Frank, 1971; Patt *et al.*, 1974).

Lange and Christiansen (1947) arrived at the diagnosis by exclusion. Cheng and Sutton (1955) showed the tumour in the right atrium by angiocardiography, and Thompson *et al.* (1977) carried out the only other cardiac catheterisation previously reported in this disease, in a 9-year-old girl. In 4 patients the diagnosis was made by tumour biopsy. While the differential diagnosis from other mesenchymal tumours may be difficult, the morphological appearances were quite characteristic in our case. In one patient the tumour was removed during operation from the outer surface of the left atrium (Hager *et al.*, 1970). This patient received cobalt-60 irradiation postoperatively and was asymptomatic at follow-up 3 years later. Two other patients have received specific treatment. Allaire *et al.* (1964) used cobalt-60 irradiation with a total of 5630 rad given over the heart, and palliation was obtained for 2 months. When, later, cyclophosphamide was added, no additional benefit was seen. Hollingsworth and Sturgill (1969) also used cobalt-60 (a total of 5400 rad) combined with vincristine and cyclophosphamide in a patient in whom the neoplasm was located at the base of the heart and over the right atrium, but with no tumour mass within the atrium. The patient tolerated the treatment well and was free of symptoms 10 months later.

In our patient the tumour, though classically located in the right atrium, did not, atypically, cause either cardiac tamponade or right-sided inflow obstruction. The continuous murmur over the tumour was not heard before admission and has not been described in any other of the published cases. Such a murmur may have been missed, since it was located well away from the usual sites of auscultation. The increase in oxygen saturation between the venae cavae and the pulmonary artery suggests a direct communication between the highly vascularised tumour and the right-sided chambers. Angiocardiography showed no evidence of septal defects, but indicated an area of dense arterialisation in the tumour suspected area when the contrast material was passing the aorta.

Irradiation and chemotherapy were started late in the course of the disease, but palliation was obtained for only 2 months, owing mainly to the direct cobalt-60 irradiation of the heart and the metastases in the left lung.

Our experience, therefore, confirms the impression that irradiation therapy has at least a palliative effect in the treatment of haemangioendotheliosarcoma of the heart.

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Operative treatment of cerebral arteriovenous aneurysm of vein of Galen complicated by congestive heart failure

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SUMMARY A rare cause of congestive heart failure in the neonatal period is an intracranial arteriovenous malformation, but this condition should be borne in mind when there is unexplained right-sided congestive heart failure. A case is reported of an aneurysm of the great vein of Galen, complicated by congestive heart failure. Successful surgical treatment was carried out using a two-stage procedure.

Intracranial arteriovenous malformations are a rare cause of congestive heart failure during the neonatal period. Both conservative and active surgical treatment of these malformations involves considerable risk (Gomez *et al.*, 1963; Holden *et al.*, 1972; Amacher and Shillito, 1973; Cunliffe, 1974; Long *et al.*, 1974; Yasargil *et al.*, 1976; Lang *et al.*, 1977).

Case report

Our patient, a girl, is now 20 months old. The birth was normal, birthweight was 3000 g, and length 50 cm; the head circumference was normal (35·2 cm). Three days after birth the patient was transferred to the Paediatric Department of the Odense University Hospital, because of a tendency

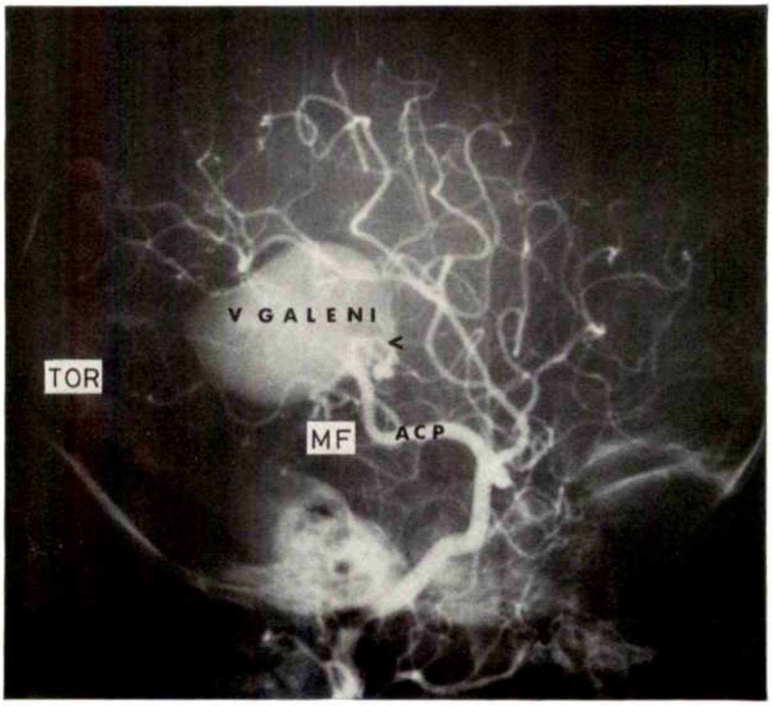

Fig. 1 *Right-sided carotid arteriogram, lateral projection. Two smaller feeders can be seen (<), in addition to the main feeder artery (MF) arising from the posterior cerebral artery (ACP). Note the large torcular (TOR).*

to regurgitate feeds.

The infant was hypotonic, tachypnoeic, pale-greyish in colour, and jaundiced; the neck veins were congested, and there was hepatomegaly. The first and second heart sounds were split and there was a soft early systolic murmur in the third and fourth intercostal spaces. *X*-ray film of the chest showed an enlarged heart and an electrocardiogram showed right-sided hypertrophy.

The patient was treated with digoxin and diuretics. Heart catheterisation was carried out because congenital heart disease was suspected, and showed a left-to-right shunt at atrial level (pulmonary/systemic flow ratio 2·0), severe pulmonary arterial hypertension (105/47 mmHg), and a high oxygen saturation (99%) in the jugular vein at the base of the skull. These observations indicated an arteriovenous shunt in the cerebral circulation, with resulting congestive heart failure.

Further examination revealed that there was a very loud cranial bruit, synchronous with the pulse. A brain scan showed increased uptake in the midline posteriorly, around the area of the great vein of Galen. Bilateral carotid arteriography using Seldinger's technique showed opacification of a large aneurysm of the vein of Galen (approximately 5 × 5 × 5 cm). The aneurysm was fed by 3 arteries on the right side and one on the left, arising from dilated posterior cerebral arteries. There were no feeders from the anterior cerebral artery. The torcular Herophili (confluens sinuum) was extremely dilated (Fig. 1 and 2).

The condition of the child improved only slightly within the first 3 months. Therefore a right-sided basal/temporal osteoplastic craniotomy was carried out. The main feeding artery from the posterior cerebral artery, and two smaller branches entering the anterior part of the aneurysm were

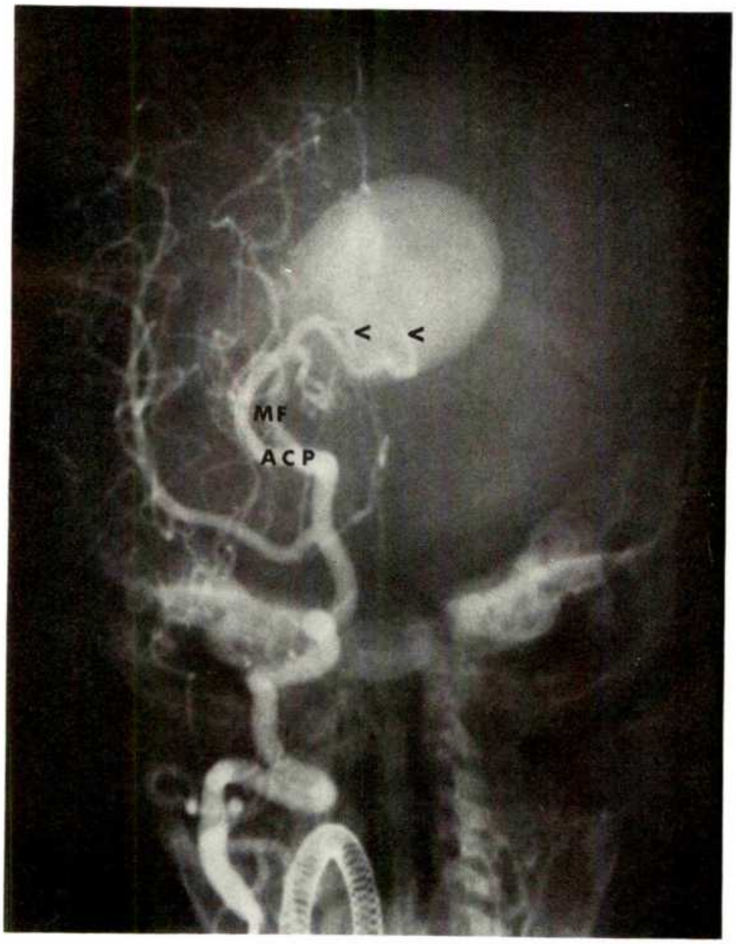

Fig. 2 *AP projection, showing the main feeder (MF) and the two smaller feeders (<) to the aneurysm of the great vein of Galen.*

exposed and ligated, using a microsurgical technique (Raimondi, 1976). No feeding arteries were seen to arise from the posterior thalamic arteries.

The postoperative course was uncomplicated, and 3 months later a left-sided basal/temporal osteoplastic craniotomy was performed with ligation of the large left-sided feeding artery. The postoperative course was uncomplicated and drug treatment was discontinued. Follow-up examination of the child at the age of 12 months and at 20 months disclosed no signs of hydrocephalus, and the cranial bruit had disappeared. The child was 3 SD below normal weight, but this was 0·5 SD more than her weight at the age of 3 months. Her mental condition was normal for age. A brain scan was normal and chest *x*-ray revealed a heart of normal size.

Discussion

Aneurysms of the great vein of Galen are divided into two groups: (1) solitary, with a direct arterial supply to a dilated vein of Galen, and (2) arteriovenous malformations which drain into the great vein of Galen (Litvak *et al.*, 1960). The feeding arteries arise from the posterior cerebral, the superior cerebellar, the anterior cerebral, or most commonly from the posterior thalamic arteries. Our patient had a malformation of the first type. Sÿmptoms are noted in early childhood. The most common clinical feature is probably hydrocephalus, resulting from direct pressure of the aneurysm on the midbrain, thus producing aqueductal stenosis. The most dangerous clinical effect, however, is the arteriovenous shunt, which overloads the heart, with resulting heart failure. The cerebral circulation in these patients may comprise 80 per cent or more of the cardiac output, with flooding of the right side of the heart with highly oxygenated blood under high pressure (Levine *et al.*, 1962; Gomez *et al.*, 1963; Amacher and Shillito, 1973). Bleeding from an aneurysm of the vein of Galen occurs only rarely because of the very thick walls which, microscopically, resemble the dura mater (Matson, 1969).

In 1973 Amacher and Shillito reviewed 42 cases of malformations similar to ours. Fourteen neonates developed signs of congestive cardiac failure immediately after birth. Eleven of these had severe heart failure, and 10 died before an operation could be performed; the other died immediately after operation from heart failure. Three neonates had mild heart failure during the first days of life, and responded well to drug treatment. These children survived operation during the first year of life. A further 22 patients had symptoms between 1 and 12 months of age, usually hydrocephalus and seizures. Significant cardiomegaly was noted on the chest *x*-ray films of only 7 of these children, while mild cardiac failure was clinically apparent in 2 of them. In a last group of 6 older patients, from 3½ to 27 years of age, the main clinical symptom was headache, and in 2 of the children there were recurring episodes of exercise syncope. Five of these patients were subjected to operation, and 2 died after operation because of inadequate haemostasis and increased intracranial pressure. Thus, one-third of all patients were neonates with heart failure.

Though intracranial arteriovenous aneurysms are a rare cause of right-sided congestive heart failure in the neonatal period, this possible diagnosis should be borne in mind in infants with unexplained right-sided heart failure. Auscultation of the cranium, with phonocardiographic recordings, can be of diagnostic importance. Heart catheterisation and cerebral angiography should confirm the diagnosis.

Our aim when treating these children is to reduce the size of the arteriovenous shunt, and operative treatment is therefore the method of choice. This involves careful clipping of all the arterial feeders. Access to these may be very difficult with conventional techniques, because of the deep-seated position of the malformation. A microsurgical technique is therefore an essential part of the operative treatment; with this there is minimal retraction of brain tissue and a well-illuminated operative field, which ensures a much safer operative course than was possible only a few years ago.

Our patient had no signs of hydrocephalus and the cerebral condition was apparently good. The angiographic studies showed that the aneurysm was fed by branches of the posterior cerebral arteries on both sides. There were no arterial feeders from the anterior cerebellar or posterior thalamic arteries and we, therefore, decided to use the two-stage procedure as described by Raimondi (1976). The advantages of this method are easy access to the feeding arteries and, by the use of the two-stage procedure, a gradual reduction in the arteriovenous shunt, thus lessening the risk of postoperative complications (Amacher and Shillito, 1973; Long *et al.*, 1974; Raimondi, 1976; Yasargil *et al.*, 1976). The postoperative course was quite uneventful and the child is developing normally after more than 20 months of observation.

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Requests for reprints to Dr Kaj Lillquist, Paediatric Department H, Odense Hospital, 5000 Odense, Denmark.

British Heart Journal, 1979, **42**, 742–745

Congenital cardiac abnormalities in monozygotic twins

Report and review of the literature

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SUMMARY A pair of monozygotic twin girls is reported with concordance for 3 congenital cardiac abnormalities: (1) secundum atrial septal defect, (2) aneurysm of the membraneous ventricular septum, and (3) electrocardiographic frontal plane left axis deviation.

A review of the published materials shows a 9·5 per cent incidence of concordance for congenital heart disease among monozygotic twins. In those in whom a precise cardiological diagnosis was made, 15/16 pairs (95%) were concordant for a specific defect, 2 had an additional defect, and only 1 pair had completely dissimilar defects.

Concordance for congenital heart disease in monozygotic twins is uncommon, but when it occurs the defects will most often be identical.

The study of twins can provide information pertinent to the aetiology of congenital heart diseases. Several previous studies have noted the surprising lack of concordance for congenital heart malformations in monozygotic twins (Uchida and Rowe, 1957; Nora *et al.*, 1967; Anderson, 1976). The purpose of this communication is to report a unique pair of monozygotic twins in whom secundum atrial septal defect, aneurysm of the membraneous ventricular septum, and frontal plane electrocardiographic left axis deviation were identified in each patient. This prompted a review of the published reports on the inheritance of congenital heart disease and the specificity of phenotypic expression.

Case report

J. D. and K. D. were 11-year-old twin girls referred to the National Heart, Lung, and Blood Institute for diagnosis and treatment of congenital heart disease. The patients were products of an uncomplicated, full-term spontaneous vaginal delivery of a gravida 6, para 6, 34-year-old mother. Both parents were of Southern Italian ancestry. At birth both girls were noted to be small relative to gestational age. Both children achieved normal psychomotor development and were without any non-cardiac developmental anomalies. K. D. was entirely asymptomatic while J. D. began to note dyspnoea on severe exertion 6 months before admission.

Family history revealed that the mother had died suddenly of unknown causes 2 years before admission. The propostii had 7 additional sibs, including a set of fraternal female twins aged 17 years. Non-invasive cardiac evaluation including physical examination, electrocardiogram, chest *x*-ray film, and echocardiogram showed no evidence of heart disease in the fraternal twins, the father, and 5 sibs. Two other sibs were unavailable for examination, but neither had a history of heart disease and both were found fit for military service.

On physical examination the patients were identical in appearance: they weighed 19 kg and were 127 cm tall (both in the first centile for age). Monozygosity was further confirmed by the establishment of concordance for 18 red blood cell antigens (calculated probability of monozygosity of greater than 0·99 (Smith and Penrose, 1955)). Arterial pulses and jugular venous pressures were normal. Both children had a parasternal right ventricular lift and only minimal (0·02 s) respiratory variation of a widely split S_2. K. D. had a grade 3/6 systolic ejection murmur along the left sternal border, and J. D. had a louder, longer, grade 4/6 holosystolic murmur localised to the lower left sternal border. Neither child had physical findings indicative of heart failure. Electrocardiograms (Fig. 1) showed normal sinus rhythm, left axis deviation of −60° with a counterclockwise loop in the frontal plane, and an rSR′ pattern in lead V1. Chest radiographs revealed mild dilatation of the

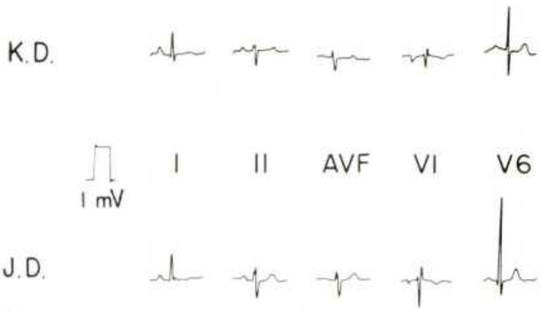

Fig. 1 *Selected electrocardiographic leads from twins K. D. and J. D., showing left axis deviation in the frontal plane and an rSR' pattern in lead V1.*

main pulmonary artery segments and increased pulmonary vascular markings consistent with left-to-right shunt. Cardiac catheterisation showed normal to slightly raised pulmonary arterial pressures (J. D. 35/13 mmHg, mean 24 mmHg; K. D. 28/14 mmHg, mean 22 mmHg); other intracardiac pressures were within normal limits. Both children had large left-to-right shunts at the atrial level, as determined by oximetry and dye dilution curves. Pulmonary to systemic flow ratio was 2·3 in J. D. and 3·3 in K. D. Left ventricular cineangiography (Fig. 2) showed opacification of the right ventricle across a small membraneous infracristal ventricular septal defect in J. D. and a small aneurysmal outpouching, with a smooth wall and wide neck in the same region of the ventricular septum without apparent intraventricular communication in K. D.

At operation each patient was found to have an identical, 1 × 2 cm, secundum atrial septal defect which was closed with a Teflon patch. In addition, they were found to have had identical aneurysms of the membraneous ventricular septum. In J. D. the aneurysm had a 3-mm diameter opening in its apex which was closed with a single suture. The girls recovered uneventfully from operation. Six months after operation both patients were asymptomatic, and recatheterisation showed normal right heart pressures with no evidence of residual intracardiac shunt.

Discussion

Both members of the monozygotic twinship described in this report manifested a complex of three essentially identical congenital cardiac abnormalities. The haemodynamically important part of this complex was a secundum atrial septal defect, with a large left-to-right shunt. The second part of the complex was an aneurysm of the membraneous portion of the ventricular septum, which contained a small intraventricular communication in one of the twins (J. D.). Though it is likely that K. D. also had an intraventricular communication through the region of the aneurysm earlier in her course, which closed spontaneously (Varghese *et al.*, 1966), this point remains speculative. The third part of the complex was the finding in the electrocardiogram of frontal plane left axis deviation consistent with the diagnosis of the left anterior hemiblock (Rosenbaum *et al.*, 1970).

The complex represents a rare combination of anomalies. Less than 5 per cent of patients with secundum atrial septal defects are reported to have left axis deviation on the electrocardiogram (Harrison and Morrow, 1963), and less than 10

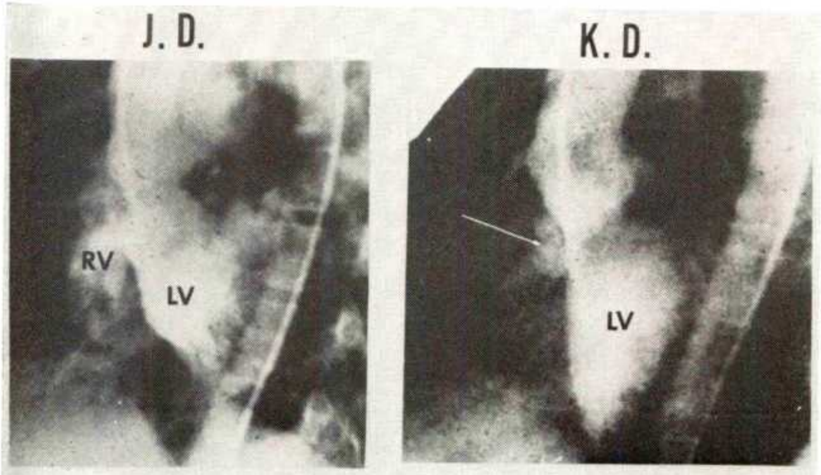

Fig. 2 *Left ventricular (LV) cineangiogram in the 70° left anterior oblique projection showing early opacification of the right ventricle (RV) across a high ventricular septal defect in J. D., and an aneurysm of the ventricular septum (white arrow) without interventricular shunting in K. D.*

per cent of patients with membraneous ventricular septal defect have associated atrial septal defect (Girod *et al.*, 1966).

Table 1 *Prevalence of concordance for congenital heart disease in twinships*

Author	*Monozygotic*	*Dizygotic*	*Total*
Ross (1959)	2/9	2/26	4/35
Nora *et al.* (1967)	6/13	1/24	7/37
Anderson (1977)	4/59	1/43	5/102
Kenna *et al.* (1975)	2/15	2/12	4/27
Menashe *et al.* (1967)	0/15	0	0/15
Uchida and Rowe (1957)	0/13	0/13	0/26
Lamy *et al.* (1957)	0/7	1/9	1/16
Leck *et al.* (1965)	0/*	1/*	1/22
Campbell (1961)	0/12	0/4	0/16
Myrianthopoulos (1975)	1/6	0/1	1/7
Hay and Wehrung (1970)	5/59	2/69	7/128
Total	20/208 = 9·5%	9/201 = 4·5%	30/431 = 7·0%

* Number MZ and DZ twins not reported; number not included in totals.

Despite identical genotype and near identical prenatal environment, the incidence of concordance for congenital heart disease in monozygotic twins is low. Table 1 sets out 11 series representing 208 monozygotic twins and 201 dizygotic twins, selected for the presence of congenital heart disease in one member of the twinship. The prevalence of concordance for any congenital heart disease was 9·5 per cent in the monozygotic twins and 4·5 per cent in the dizygotic twins. Only 5 of the series reported sufficient data to allow an analysis of the specific cardiac defects (Table 2). When a monozygotic twinship was concordant for congenital heart disease, there was a 94 per cent incidence for concordance for the specific defect. While additional defects may be present in a co-twin, only one pair was reported to have completely different defects. Therefore, excluding complex fused hearts, 10/100 (10%) of completely diagnosed monozygotic twins were fully (specific defect) concordant.

As emphasised by Nora *et al.* (1967), the genetics of congenital heart disease rarely conforms to either a typical Mendelian (for example, Hurler's syndrome) or chromosomal (for example trisomy 21) mode of inheritance. Most often the aetiological mechanism appears to be multifactorial, representing an interaction between a genetic threshold of liability and environmental factors of variable potency (Falconer, 1977).

Both the atrial septum secundum and the membraneous ventricular septum are formed in the fifth to seventh week of gestation (Warkany, 1971), with the cardiac specialised conduction system being formed somewhat earlier (Davies, 1971). In the family described here the hereditary predisposition toward congenital heart disease did not appear strong in that none of the remaining 7 children or the father have any known evidence of congenital heart disease. Hence environmental factors may have played an important role in the abnormal prenatal development of these twins.

The authors wish to thank Drs Jeffrey S. Borer, Barry J. Maron, and Stephen E. Epstein for the clinical care and evaluation of these patients.

Table 2 *Concordance for specific defects in monozygotic twins with congenital heart disease*

Author	*Number concordant with CHD/number MZ twins*	*Number concordant for specific defect*	*Number concordant for specific plus additional defects*	*Number nonconcordant for specific defects*
Ross (1959)	2/9	1 PDA		1 (A) ASD (B) VSD
Nora *et al.* (1967)	6/13	5 ASD VSD TOF PS PDA	1 (A) ASD, VSD (B) ASD, PDA, COA	
Anderson (1977)	4/59	3 HLH PABS FCH	1 (A) PVS (B) PVS, VSD	
Kenna *et al.* (1975)	2/15	2 PDA VSD		
Myrianthopoulos (1975)	1/6	1 FCH		
Total	15/102	12	2	1

ASD, atrial septal defect; VSD, ventricular septal defect; PDA, persistent ductus arteriosus; TOF, tetralogy of Fallot; PS, pulmonary stenosis; PABS, pulmonary artery branch stenosis; HLH, hypoplastic left heart; FCH, fused complex heart; COA, coarctation of aorta; MZ, monozygotic; DZ, dizygotic.

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Notices

British Heart Journal, 1979, 42, 746–747

J. C. Banerjee

Dr Jogesh Chandra Banerjee, who died recently in Calcutta, was a pioneer in the field of cardiology in India. He was director-professor of medicine at Calcutta Medical College and, after retirement in 1966, became Emeritus-professor in the same College. He was a past president of the Cardiological Society of India, having been one of its founder members, a Director of the All India Heart Foundation, and Editor of the *Indian Heart Journal* for many years. He was a reputable clinical cardiologist and published several papers on the prevalence of rheumatic heart disease and its various manifestations in Bengal. He trained many generations of students in clinical cardiology, and received the highest national award of Padma Bhushan in 1964. He was 79 years of age.

International Society and Federation of Cardiology, Geneva

The International Society and Federation of Cardiology (ISFC) has an intensive programme of scientific and public educational activities. These activities include the work of its public education committee and of its scientific councils on arteriosclerosis; cardiomyopathies; epidemiology and prevention; hypertension; paediatric cardiology; rehabilitation of cardiac patients; thrombosis and haemostasis. A new scientific council on cardiac metabolism is being formed. Members of these councils act as advisers to the Public Education Committee.

The scientific councils organise multinational research studies, teaching seminars, and postgraduate courses on such subjects as congestive cardiomyopathies, endomyocardial fibrosis, mild hypertension, epidemiology, and prevention of cardiovascular disease. Task forces are being formed to examine the current position of thrombosis and drugs which inhibit platelet function, and other urgent issues. Teaching and research fellowships are planned, and an annual international lectureship is in prospect.

In collaboration with the World Health Organisation, task forces have been working on proposed international classifications and definitions of arrhythmias, ischaemic heart disease, cardiomyopathies, and haemodynamics. The first two task forces have already issued their reports*, while those on cardiomyopathies and haemodynamics are under preparation.

A manual on the control of hypertension for general practitioners is being prepared, also in collaboration with WHO.

Close liaison is maintained with WHO in the field of public education and prevention. Workshops and conferences have been held in 1979 and are being arranged in 1980 to emphasise the cardiovascular dangers of cigarette smoking.

The ISFC sponsors world congresses of cardiology, which are held every four years, and participates in the planning of the scientific programme.

Further information may be obtained from the ISFC Geneva Office, PO Box 117, 1211 Geneva 12, Switzerland.

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* Definition of terms related to cardiac rhythm. Report of a WHO/ISFC Task Force. Published in *Am Heart J* 1978; **95:** 796–809, and in *Eur J Cardiol* 1978; **8/2:** 127–44, and in French in *Arch Mal Coeur* 1979, Suppl. (June). Part II: Classification of cardiac arrhythmias and conduction disturbances—*Am Heart J* 1979; **98:** 263.

Nomenclature and Criteria for Diagnosis of Ischemic Heart Disease. Report of the Joint ISFC/WHO Task Force on Standardisation of Clinical Nomenclature. *Circulation* 1979; **59:** 607–9 (French version will be published in *Arch Mal Coeur*).

World Congress of Paediatric Cardiology

To mark the coming of age of paediatric cardiology as a speciality, a World Congress of Paediatric Cardiology will be held in London between 2 and 6 June 1980 at the Wembley Conference Centre.

A reduced fee is available for registrations received before 1 February 1980. For further information please contact the Secretary General, Professor Fergus Macartney, The Hospital for Sick Children, Great Ormond Street, London WC1 3JH.

VIIIth Congress of International Primatological Society

Symposium on 'Regression of atherosclerosis in non-human primates' at the VIIIth Congress of the International Primatological Society, Florence, Italy, 5 July 1980.

For details apply to: M R Malinow, Oregon Regional Primate Research Center, 505 NW 185th Avenue, Beaverton, Oregon 97005, USA.

Symposium on Critical Care and Pulmonary Medicine

Second international symposium on computers in critical care and pulmonary medicine will take place at Lund, Sweden, from 3–6 June 1980.

Correspondence regarding abstracts, papers, registration, and symposium accommodation should be sent to: Miss Bodil Richardson, Symposium Secretary, Kliniskt Fysiologiska Avdelningen (Department of Clinical Physiology), Lasarettet, S-221 85 Lund, Sweden.

Platelet-acting Drugs and Coronary Heart Disease

A meeting will be held at the Zoological Society, London NW1, on Tuesday 15 January 1980, under the auspices of the *International Society and Federation of Cardiology, Scientific Council on Epidemiology and Prevention.*

Inquiries to Professor G Rose, London School. of Hygiene and Tropical Medicine, Keppel Street, London WC1.

Echocardiography 1980

The conference and its accompanying Trade Exhibition will be held in Newcastle upon Tyne in September 1980, and both are being organised by Conference Services Limited.

Further information on either the conference or the exhibition is available from Conference Services Limited, 3 Bute Street, London SW7. Tel: 01-584 4226.

International Congress on Death and Dying

An International congress on death and dying will be held in Imperial College, London SW7, from 31 March to 2 April 1980.

Further details from: The Conference office, 37a Maida Vale, London W9.

World Congress of Angiology

World Congress of Angiology will be held in Athens from 7 to 12 September 1980.

Further information from: Secretary, 17 Sisini Str, Athens 612, Greece. Tel: 721 633.

References

Contributors should note that, in future, references in the text of papers submitted to this journal and in the bibliography should be prepared in the new format, as outlined briefly in the Notice to contributors.

Full details of this new, uniform style, which was agreed at a meeting of the International Steering Committee of Medical Editors held in Vancouver, were published in the *Br Med J* (1979; **1**: 532–35) and *Ann Intern Med* (1979; **90**: 95–9). Reprints of this article are available from the *Br Med J* (price 50p).

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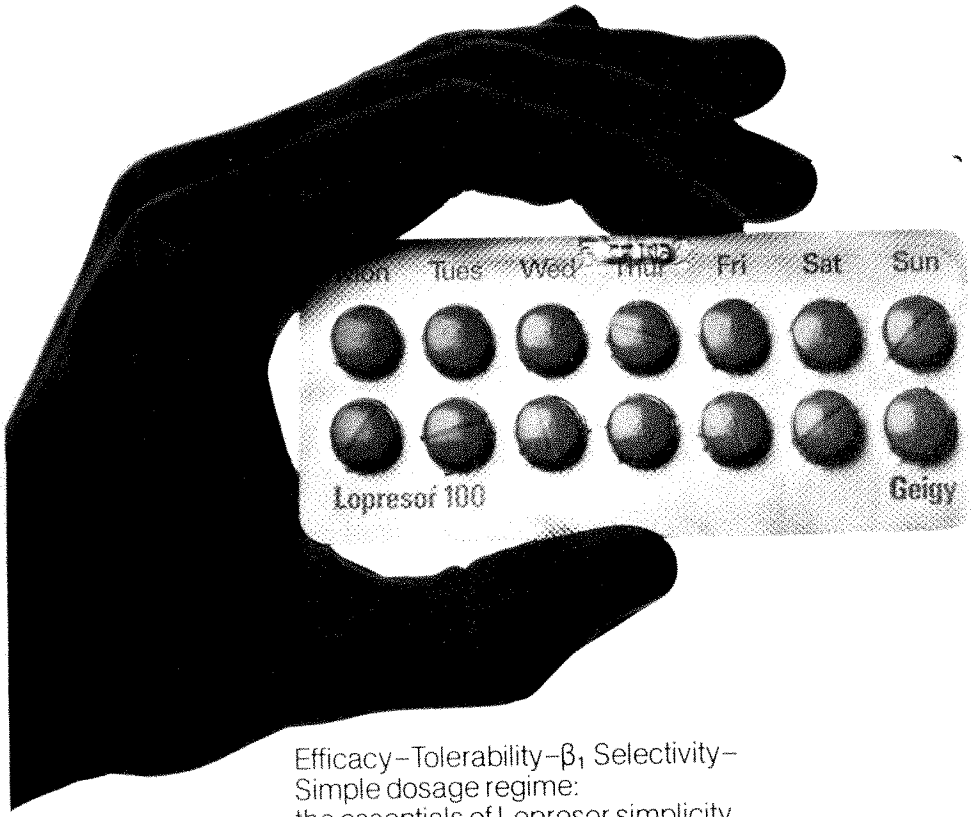

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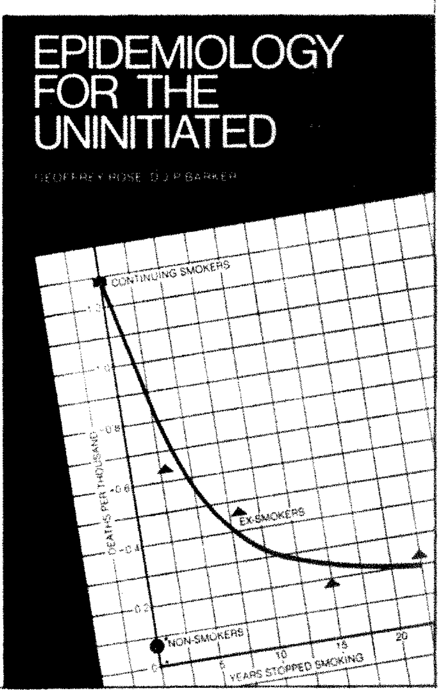

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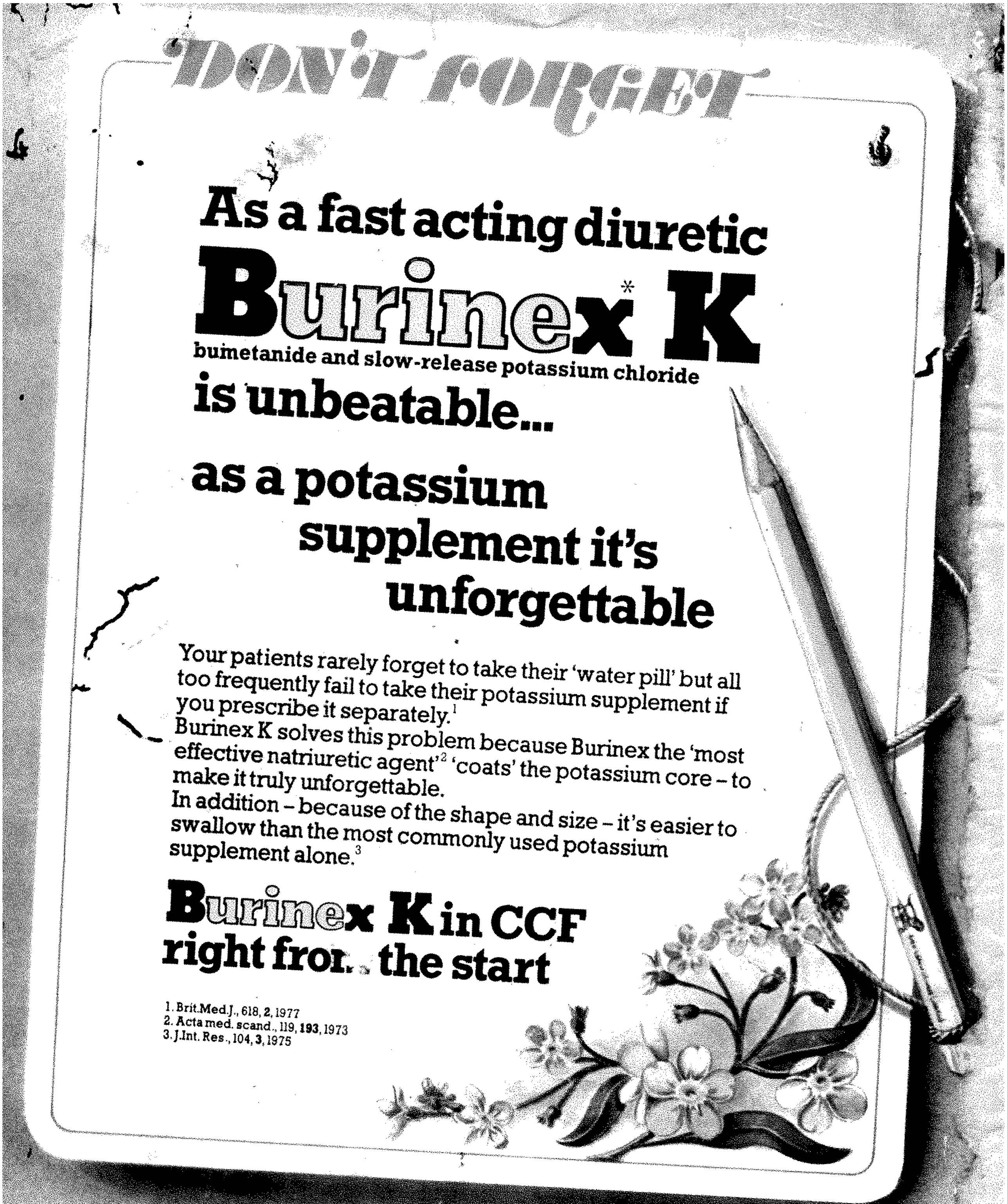

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